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DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 100

New Drug Approval Process

Third Edition

The Global Challenge

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Drug Development Teams

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I. INTRODUCTION

The drug discovery and development process requires the close interaction of a large number of scientific disciplines for as many as 10 or 12 years. Most pharmaceutical and biotechnology firms employ teams to guide the processes involved in taking a discovery through the various drug development stages and making the drug candidate into a therapeutic product. The responsibilities of these project teams include, but are not limited to:

1. Reviewing research results from experiments conducted by any of the various scientific disciplines
2. Integrating new research results with previously generated data
3. Planning research studies to further characterize a drug candidate
4. Preparing a detailed drug development plan, including designation of key points or development milestones, generating a timeline for completion, and defining the critical path
5. Monitoring the status of research studies to ensure that they are being conducted according to the timeline and critical path in the development plan and, if appropriate, modifying the plan as new information becomes available
6. Comparing research results and development status and timelines with drug candidates under development by competitors
7. Conducting appropriate market surveys to ensure that the development of a drug candidate is economically justified and continues to meet a medical need
8. Reporting the status of the drug development program to management

and making recommendations on the continued development of the drug candidate

This chapter discusses the various types of project teams that are involved in the drug discovery and development process. It also provides a detailed example of a drug development logic plan for what many developmental pharmaceutical scientists consider to be the most difficult and time- and resource-consuming drug candidate to develop into a therapeutic product.

II. DRUG DISCOVERY PROJECT TEAM

A company makes a decision to enter into a new disease area or to expand an existing therapeutic area on the basis of new research findings, an unmet medical need, or marketing surveys. The responsible department, commonly a therapeutic disease group such as cardiovascular, CNS, cancer, infectious diseases, or metabolic diseases, assigns researchers to the new project—usually chemists to synthesize compounds and pharmacologists or biologists to evaluate the leads in in vitro or in vivo models of the disease. This small group of researchers is the first project team and is commonly called a discovery project team. Their primary responsibility is to identify lead compounds or classes of compounds worthy of continued research. The initial effort may consist of screening existing compounds in the company's archives or libraries of compounds, obtained by use of combinatorial chemistry techniques, for activity. The primary endpoint used in this assessment is the potency of the various lead compounds in the disease model. The pharmacology results are shared with the chemists, who then prepare analogues of the most active compounds to explore further the SAR.

Once a lead or class of leads has been identified, the discovery team commonly grows to include other scientific disciplines to characterize more fully the possibility of developing the leads of interest. The other disciplines include, but are not limited to:

1. Analytical chemistry to define the physical and chemical properties of the leads and to provide preliminary information on the stability of the drug substance
2. Drug metabolism and pharmacokinetics, which normally include bioanalytical chemistry, to assess the delivery and disposition profile of the leads in animal models using the route of administration projected for clinical studies
3. Toxicology to evaluate the potential for the leads to cause adverse events in in vitro and in vivo models of the disease
4. Biopharmaceutics to study the formulation potential of the leads and

to ensure that the compounds can be effectively delivered by the proposed route of administration

The results from the preliminary studies conducted by these disciplines are integrated with the biological activity data from the pharmacologist. If stability, delivery, metabolism, or toxicity problems are encountered, the chemists use the previously generated SAR information to modify the structure of the lead without destroying the site(s) required for biological activity of the compound. The new compounds are evaluated for potency and to ensure that the undesirable structural attribute, which causes the developability problem, has been deleted or minimized. Then, the other scientific disciplines check the new lead(s) to ensure that the change did not adversely affect desirable characteristics and did substantially alter the previously defined undesirable characteristics. This iterative process continues until a lead compound (or a small group of leads) is identified.

The discovery project team compiles the generated information and presents the results to management. At this stage, the drug discovery team normally recommends that a lead candidate be entered into formal preclinical development. However, that is not always the case. In the experience of this author, the results from the various scientific disciplines can be at odds with each other, with one group pushing for continued development while another thinks the potential for successful development is too low to justify the expenditure of additional resources. For example, the discovery and development of renin inhibitors as antihypertension agents were, and in some cases still are, conducted by a number of pharmaceutical companies. The discovered leads, which were structurally modified small peptides, were very potent in inhibiting renin and thus interfering with the renin-angiotensin cascade, resulting in an antihypertension effect. However, biological activity correlated and increased with lipophilicity. The most potent leads had few, if any, polar groups to provide aqueous solubility, preventing the compounds from being delivered to the intestinal wall for absorption. When absorption enhancers were used to administer the leads to animal models of hypertension, the compounds had bioavailability sufficient to reduce blood pressure. The results from drug delivery and pharmacokinetic evaluations of these same leads showed very low absorption, usually less than 10%, which was also quite variable, at times more than 200% of the amount absorbed. This difference in the developability potential of renin inhibitors caused a number of pharmaceutical companies to stop research in this area, whereas other companies continued their efforts to find inhibitors with acceptable delivery characteristics and without unacceptable decreases in potency. This effort has been successful with a new generation of renin inhibitors now in development.

Once the discovery project team's recommendation for preclinical development of a lead candidate is accepted by management, this team is either disbanded or continues their efforts to discover other compounds with attributes that could identify a next-generation lead. Many of the discovery project team members become members of the more formal preclinical development project team.

III. PRECLINICAL DRUG DEVELOPMENT PROJECT TEAM

One of the first tasks after management's acceptance of a lead candidate as a drug candidate is the establishment of the preclinical drug development team. Commonly, the researchers from the various scientific disciplines involved on the discovery project team are assigned by their departments to the new team, but not always. Some companies have defined groups that support discovery research and others that conduct nonclinical and clinical developmental studies. In this case, the newly assigned project team member needs to be "brought up to speed" by the researcher who had been providing support to the discovery team. This approach allows departments to separate the nondefinitive, or non–GLP-regulated, discovery research effort from the more definitive, or GLP-directed, drug development effort and to develop researchers with expertise in one or the other area. However, complete transfer of knowledge and experience is not always possible, and "ownership" of and "champions" for a particular compound or disease area are lost. Having the same researcher or research group involved in all aspects of the drug discovery and development process provides continuity of effort but requires a possible dilution of scientific expertise. The best approach, each of which has its attributes and demerits, has been under discussion at pharmaceutical houses for years. It will probably continue to be a point of contention for researchers wanting to develop a specific expertise or to be involved in all aspects of the drug discovery and development process. This problem is not as prevalent at biotechnology firms where researchers have to wear many hats and are commonly involved in many phases of the drug discovery and development process.

In addition to the scientific disciplines, e.g., pharmacology, chemistry, toxicology, drug metabolism and pharmacokinetics, and biopharmaceutics, involved on the discovery team, the preclinical drug development team has a number of new players. These new players include, among others:

1. A management-assigned project team leader and coordinator who are responsible for the development of the drug candidate
2. Regulatory affairs and quality assurance to ensure that the developmental studies meet regulatory requirements and are conducted according to regulatory guidelines

3. Clinical research to provide input into study designs so that the generated results support the proposed clinical program, and to initiate development of clinical safety and tolerance and efficacy protocols and the investigator's brochure
4. Analytical chemistry to develop assays and characterize the drug substance and drug product
5. Manufacturing to scale up the synthesis of the drug candidate and provide sufficient GLP- or CMP-quality material for regulatory-driven research studies
6. Marketing to determine that the drug candidate has a potential market niche in light of what other companies are developing or drugs that are already on the market for the disease indication

One of the first charges of the preclinical development project team is to prepare a drug development plan, which lists all the studies necessary for the successful development of a drug candidate. Based on the disease indication (life-threatening or non–life-threatening), the drug candidate type (small organic molecule or macromolecule), the length of therapy (acute or chronic), and the route of administration (oral, intravenous, dermal, pulmonary, etc.), each of the scientific disciplines prepares a list of their research studies, usually in the order to be conducted and with the predicted duration of time needed for completion. All of the studies are combined into a drug development logic plan (a sample is presented later in this chapter). The initial drug development plan is put together with key points or milestones in mind. These key points are commonly submission of an IND, completion of phase 2 clinical studies, and submission of an NDA or BLA. The first plan is very detailed for the preclinical development, with less definition for the clinical and nonclinical stages of development.

The individual department lists are combined with the studies ordered according to time required and dependence on the results from other studies. For example, before a subchronic toxicology study can be conducted, acute toxicology study results need to be available to define dose levels and frequency of dosing; sufficient GLP- or CMP-quality drug substance and drug product have to be available or will be available to dose the test species at the desired levels for the duration of the study; and acceptable analytical and bioanalytical methods should be in place to provide support for formulation assessment and toxicokinetics, which require preliminary pharmacokinetic information to determine the correct sampling times. Thus, the subchronic toxicology study does not depend only on when the toxicologist and his or her group can conduct the study, but also on when other disciplines have completed supportive research studies and are available to support the toxicology effort.

Once the development studies are listed and integrated into a logic plan, the next aspect is to develop a timeline. Based on the overall plan, each department determines when they can start a proposed study and when the results of the experiment can be expected. This information is added to the development plan, and the time to completion and to reach predefined milestones, such as filing an IND or completion of phase 2 clinical studies, are determined. The timeline identifies the critical path, that is, the research studies that are rate limiting and the department or departments involved. Commonly, the departments on the critical path are manufacturing, then toxicology, and finally clinical. Other scientific disciplines that have a key component to the development process can also be on the critical path. Normally, management and project team leadership want the development time to be as short as possible, which is only logical and justifiable, as a single day of development time for a product with projected yearly sales of $365 million is worth $1 million of revenue. In addition, once a patent has been filed, each day of development time decreases the patent life by a day, reducing the overall sales revenue for a product. Thus, departments attempt to be off the critical path unless absolutely necessary and will often modify their projected start or completion dates for studies in order to move off the critical path. The completed drug development plan is presented to, and accepted by, management.

The drug development plan has to be a living document and subject to change or modification as results from research studies become available. Unexpected or negative data will require additional studies to answer or explain more fully the observations. These additional studies will affect the development timeline and possibly the critical path. Typically, the status of a drug development project is formally presented to management on a semiannual or annual basis, provided no expected results are generated. Special meetings with management are held to present and discuss problem areas that are encountered, to make recommendations on how to overcome the problems, and for the additional resources that may be needed to solve or correct the problem areas.

One of the final responsibilities of the preclinical drug development project team is to prepare an IND and to submit the appropriate documents to the FDA or other regulatory agency. As the development of the drug candidate moves into the clinic, the preclinical project team becomes a clinical project team.

IV. CLINICAL DRUG DEVELOPMENT PROJECT TEAM

After the IND is submitted, the project team is again expanded to include new players. Some of the old players, such as chemistry and pharmacology, have decreased roles but may continue to serve on the team to provide scientific expertise when new problems arise. The roles of many project team members substantially expand. The new players and expanded roles of members include:

1. Physicians who will conduct phase 1, 2, and 3 clinical studies or serve as medical monitors if these studies are conducted by a CRO
2. Clinical research associates who coordinate and monitor the phase 1, 2, and 3 studies and ensure that the appropriate documents, such as case report forms, are correctly prepared
3. Manufacturing to coordinate the development of the drug substance and drug product production facilities and to ensure that all the necessary processes are in place
4. Quality control to ensure that the appropriate assays are developed, validated, and in place to support the manufacturing program
5. Statisticians to assist in designing clinical protocols and in evaluating generated results from both nonclinical and clinical studies
6. Clinical pharmacokinetics to support phase 1 studies and to design and conduct pharmacokinetic studies in special populations
7. Marketing to continue evaluating the status of competitor's drug candidates and the potential of the developmental candidate to fill a medical need and to prepare for product launch

The drug development plan is updated, with emphasis placed on the clinical and manufacturing aspects, either of which could be on the critical path. The nonclinical program continues but, with the exception of carcinogenicity studies, is rarely rate limiting. As the results from phase 1 and phase 2 clinical trials become available, special nonclinical or even clinical studies may be needed to evaluate clinical observations. These may include unexpected adverse events in volunteers or patients; pharmacokinetic differences between human and animal models; or correcting unforeseen problems, such as unacceptable or highly variable delivery in humans or the inability to scale up the manufacturing process using the proposed methods. For example, this author was a project team member for the development of a CNS drug candidate for anxiety. Phase 1 single-dose, dose-escalating studies in human volunteers produced no safety or tolerance issues. Thus, phase 1 multiple-dose studies were initiated, and planning for phase 2 efficacy studies started. Bioanalytical analyses of clinical specimens for the parent drug and a known metabolite showed the presence of an unidentified drug metabolite. Pharmacokinetic evaluation of the new metabolite suggested that the compound had an estimated apparent terminal disposition half-life of more than 7 days and thus would accumulate after multiple-dose administration, possibly leading to adverse events. Analogues of the parent drug candidate were prepared, and the metabolite was identified. Pharmacology testing showed the metabolite to be almost as biologically active as the drug candidate and, because of the accumulation aspect, was efficacious at lower doses. Toxicology evaluation demonstrated that the metabolite had a safety profile similar to the parent compound, and thus had a better therapeutic ratio when combined with the lower dose required for pharmacologic activity. Biopharmaceutics and pharmacokinetics showed that the metabolite had acceptable bioavailability. These results suggested that the metabolite might be a better drug candidate than the parent. A preclinical program was initiated on the metabolite and after a delay of only a few months, the metabolite entered the clinic as a drug candidate with a better chance of success than the original compound.

The final responsibility of the clinical project team is to ensure that all the research studies are appropriately documented in technical reports or scientific publications, and to compile this information, along with the necessary summaries, into an NDA or BLA submission. After submission, the project team interacts with the regulatory agency and provides answers to any questions. If requested, the project team designs and conducts the necessary research studies to support the submission. Once the NDA or BLA has been approved, the final responsibility of the clinical development team is to coordinate the launch of the new therapeutic agent.

V. DRUG DEVELOPMENT LOGIC PLAN

One of the primary functions of the project team is to coordinate the various studies necessary for the successful development of a drug candidate and to ensure that the timeline for development is on schedule. As mentioned above, this coordination is usually accomplished by preparing a detailed drug development plan and monitoring the research process. The required studies and the extent of the development plan depend on four criteria of the proposed drug candidate, which are:

1. Drug candidate type (macromolecule such as a protein, polypeptide, or oligonucleotide, or small organic molecule commonly referred to as an NCE)
2. Disease indication (life threatening such as AIDS, some cancers, some cardiovascular and CNS indications, or non-life threatening such as hypertension, diabetes, anti-inflammatory agents, antibacterial agents)
3. Therapy duration (acute, with one or a few doses being sufficient for treatment, or chronic, with prolonged administration necessary to mediate the disease process)
4. Route of administration (I.V. as a bolus injection or an infusion, or nonintravenous such as oral, pulmonary, subcutaneous, intramuscular, dermal, etc.)

These four criteria form a matrix of 16 possible drug candidate types. A generic drug development plan for what most drug development scientists consider to be the most difficult drug candidate to develop successfully is shown in the appendix. The timelines for the various studies and their integration into a formal drug development plan are compound-specific and dependent on the availability of resources within the various departments at the company. Similarly, the designation of key milestone events and the critical path are compound- and company-specific. However, the information provided in the sample logic plan can be used as a template to generate a logic plan for the other 15 drug candidate types. Depending on the drug candidate type, some of the listed studies, such as absolute bioavailability for a candidate to be administered intravenously or carcinogenicity studies for a candidate to be administered acutely for a life-threatening disease, may not be necessary. Other studies, such as biological potency and antigenicity evaluations for a macromolecule, may be required.

VI. CONCLUSION

This chapter has described the various project teams and their responsibilities, including the generation, implementation, and monitoring of a drug development plan, in the drug discovery and development process. The large number of scientific disciplines required for the successful development of a drug candidate into a therapeutic product makes the use of project teams a common practice within the pharmaceutical and biotechnology industry. The abilities of the members to communicate the results from their research efforts and to integrate the results from other disciplines into their study designs are important aspects of the project team environment.

APPENDIX: DRUG DISCOVERY AND DEVELOPMENT LOGIC PLAN EXAMPLE

Logic Plan Drug Candidate Characteristics

A.	Candidate:	New chemical entity (small organic molecular)
B.	Indication:	Non-life-threatening disease
C.	Therapy:	Chronic administration
D.	Dosing Route:	Nonintravenous

I. **Drug Discovery Stage**
   A. Chemistry or Synthesis
      1. Generate drug discovery lead(s) using rational approaches, such as random screening, nonrandom screening, drug metabolism, or clinical observations, or using combinatorial chemistry libraries.
      2. Modify lead(s) by identification of pharmacophore and synthesis of analogues; functional group changes; SAR of lead candidate

analogues; structure modification, such as homologation, chain branching, ring-chain transformation, and bioisosterism to increase potency and therapeutic ratio; and QSAR.

3. Determine drug-receptor interactions using techniques like molecular modeling and X-ray crystallography.

B. Pharmacology or In Vitro and Animal Model Efficacy
   1. Using in vitro techniques, evaluate requirements for activation and dependency on dosing schedule and route of administration; calculate inhibitory concentrations, e.g., IC_{50} and IC_{90}, for each system evaluated; assess potential for resistance to lead candidate(s); determine synergistic, additive, or antagonistic drug-drug interactions during combination therapy, if appropriate; evaluate possible cytostatic or cytotoxic concentrations of lead candidate(s) on various cell types (bone marrow, stem cells, and immune system cells).
   2. Define and characterize an animal model(s) that mimics the human disease to be evaluated and determine appropriate end points for assessment of biological activity.
   3. Evaluate in vivo dose-response range, including dose-response comparison of lead candidates; calculation of pharmacologically active doses, e.g., ED_{50} or ED_{10}; and therapeutic ratio when combined with no effect or minimum toxic effect dose level.
   4. Conduct other in vivo evaluations including, but not limited to, dosing regimen dependency; route of administration and formulation dependency; and spectrum of activity, disease status, cross-resistance profile, combination therapy for synergy or antagonism, and special models.

II. Drug Developability Stage

A. Preliminary Formulation Evaluation
   1. From pharmacology results and proposed clinical program, select route of administration (oral, pulmonary, intramuscular, subcutaneous, transdermal, ocular, vaginal, buccal, sublingual, etc.) and formulation type to be dosed (solution, suspension, tablet, capsule, granulation powder, microspheres, microemulsion, depot drug, etc.).
   2. Evaluate excipients, including concentration and potential for interaction.
   3. Select and evaluate formulation process(es), such as tabletting, granulation, lyophilization, or microencapsulation.
   4. Prepare prototype formulation.
   5. Confirm formulation composition, including, but not limited to, drug substance content, drug substance stability, excipient levels, water, and residual solvents, using appropriately characterized methods.

6. Measure formulation physical properties, such as hardness, size, size distribution, morphology.
7. Measure formulation function, such as release or disintegration profile and nonrelease properties like taste-masking.
8. Develop and characterize stability-indicating analytical method.
9. Define and implement preliminary stability studies on drug substance and proposed drug product.

B. Preliminary Bioanalytical Method Development
    1. Select bioanalytical technique (HPLC, GC, LC-MS, ELISA, etc.).
    2. Select physiologic matrix (plasma, serum, whole blood, urine).
    3. Characterize bioanalytical method, including sample preparation procedure, for linearity, sensitivity, specificity, precision, and accuracy.
    4. Conduct preliminary stability study of drug candidate in selected physiologic matrix(ces).

C. Pilot Pharmacokinetic and Bioavailability Assessments
    1. Evaluate distribution and disposition in pharmacology animal model species after I.V. and proposed route of administration.
    2. Evaluate pharmacokinetics and bioavailability (drug delivery) in toxicology rodent and nonrodent animal species after I.V. and proposed route of administration.

D. Toxicology
    1. Evaluate single-dose or dose-escalation acute toxicity in rodent species.
    2. Evaluate single-dose or dose-escalation acute toxicity in nonrodent species.

III. Preclinical Drug Development Stage

A. Drug Candidate Characterization
    1. Validate stability-indicating analytical method.
    2. Generate impurity profile and identify impurities in drug substance and drug product.
    3. Study stress stability for drug substance and proposed drug product.

B. Formulation Development
    1. Review preliminary pharmacokinetics and histology (local reaction) results and modify formulation, if necessary, using GLP- or GMP-quality drug substance.
    2. Characterize and optimize modified formulation for excipients, pH, processing, etc.

C. Bioanalytical Method Validation
    1. Validate developed method for specificity, sensitivity, range of reliable results, precision, and accuracy for each physiologic matrix type and for each species.

   2. Evaluate protein binding in animal species and humans.
   3. Determine drug candidate stability in selected physiologic matrices from time of collection to time of assay.

D. IND-Directed Toxicology Studies
   1. Determine safety pharmacology profile in central nervous, cardiovascular, respiratory, renal, and gastrointestinal systems.
   2. Evaluate genetic toxicology.
   3. Conduct local irritation studies.
   4. Determine occupational toxicology (dermal, eye irritation, skin sensitization).
   5. Perform subchronic (2- or 4-week) study in rodent using proposed clinical route of administration. Study should have a toxicokinetic component.
   6. Perform subchronic (2- or 4-week) study in nonrodent using proposed clinical route of administration. Study should have a toxicokinetic component.
   7. Perform subchronic (13-week) study in rodent species using proposed clinical route of administration. If appropriate, include a toxicokinetic component.
   8. Perform subchronic (13-week) study in nonrodent species using proposed clinical route of administration. If appropriate, include a toxicokinetic component.
   9. Design and conduct additional confirmatory or specialized studies, as warranted.

E. Pharmacokinetics and Drug Metabolism
   1. Evaluate absolute bioavailability, distribution and disposition, and linearity of kinetics over toxicology dose range, i.e., dose proportionality, in pharmacology and toxicology animal species.
   2. Synthesize and characterize radiolabeled drug candidate.
   3. Using radiolabeled drug candidate, determine mass balance, including metabolite profiling and route(s) of elimination, in toxicology animal species.
   4. Correlate in vitro metabolism using liver and other appropriate enzyme systems from animal models and humans.
   5. Provide toxicokinetic support to toxicology studies.

F. Mechanism of Action Studies
   1. Study effect on cell cycle or replication cycle.
   2. Determine intra- or extracellular site of action.
   3. Evaluate requirements for enzyme activation or inhibition for desired pharmacologic response.
   4. Perform enzyme-substrate kinetic studies, if appropriate.

    5. Assess intracellular site of action using compartmentalization experiments.

IV. Nonclinical Drug Development Stage (conducted concurrently with Clinical Development)

- A. Manufacturing Program
    1. Obtain COAs on raw materials.
    2. Validate formulation process procedures such as mixing, sterilization, lyophilization, closure, resolubilization.
    3. Write CMC section for IND.
    4. Make phase 1 clinical supplies using GLP or CMP process.
    5. Test clinical supplies for composition, required characteristics, and function.
    6. Release phase 1 clinical supplies to clinic.
- B. Quality Control Processes
    1. Validate analytical method(s) for drug substance, including impurity profile.
    2. Validate analytical method(s) for drug product, including impurity profile.
    3. If appropriate, validate analytical method(s) for key intermediates in manufacturing process.
- C. Chronic and Reproductive Toxicology
    1. Conduct chronic (6-month) nonrodent toxicology study.
    2. Conduct chronic (6-month) rodent toxicology study or combined rat chronic toxicity/carcinogenicity (2-year) study.
    3. Perform mouse carcinogenicity study, if necessary.
    4. Evaluate reproductive/development toxicity in rats or other appropriate rodent species (Segments I, II, and III).
    5. Evaluate reproductive/development toxicity in rabbits or other appropriate nonrodent species (Segment II).
    6. Design and conduct additional confirmatory or specialized studies, as warranted.
- D. Pharmacokinetics and Drug Metabolism
    1. Using radiolabeled drug candidate, perform tissue distribution, with whole body autoradiography, in rodents after single-dose and multiple-dose (if appropriate) administration.
    2. Provide toxicokinetic support if necessary, including, but not limited to, feto-placenta transfer and lacteal secretion studies to support reproductive toxicology.
    3. Isolate and identify metabolite(s), if appropriate, in toxicology animal species and humans.
    4. Evaluate pharmacokinetics of metabolite(s) to support pharmacologic and toxicologic evaluation of metabolites, if appropriate.

5. Conduct in vitro and in vivo enzyme-induction and enzyme-inhibition studies in animal models, if appropriate.

E. Mechanism of Action
   1. Conduct additional mechanism of pharmacologic action studies, if necessary.
   2. Conduct additional mechanism of toxicologic action studies, if necessary.

F. Clinical
   1. Prepare phase 1 clinical protocol.
   2. Prepare investigator's brochure.
   3. Prepare and submit IND to regulatory agency.

V. **Clinical Drug Development Stage (conducted concurrently with Nonclinical Development)**

A. Phase 1 Safety and Tolerance Study
   1. Obtain IRB approval for phase 1 study.
   2. Prepare and release clinical supplies.
   3. Develop and validate bioanalytical method for drug candidate and known metabolites in human physiologic fluid specimens.
   4. Conduct single-dose and multiple-dose escalation evaluation of drug candidate in normal human volunteers.
   5. Study pharmacokinetics of drug candidate and known metabolites in human after single-dose and multiple-dose administration.
   6. Develop and validate surrogate and biochemical marker bioanalytical method(s), if appropriate.
   7. Design and conduct mass balance study in human volunteers using an appropriately labeled drug candidate.

B. Phase 2 Efficacy Studies
   1. Prepare phase 2 efficacy study protocols and obtain IRB approval.
   2. Conduct multiple-dose evaluation of drug candidate efficacy in patients with disease indication.
   3. Determine surrogate and biochemical marker levels in human physiologic fluid specimens.
   4. Design and conduct bioequivalence studies if drug product used in phase 2 is changed for phase 2 and 3 clinical trials.

C. Phase 3 Definitive Safety and Efficacy Studies
   1. Prepare phase 3 clinical protocols and obtain IRB and regulatory agency approvals.
   2. Conduct randomized, double-blind, placebo-controlled studies in patients with disease indication using at least two dose levels of drug product.
   3. Perform pharmacokinetic studies in special populations (geriatric

or pediatric age groups, renal or hepatic impaired patients, and drug-drug interaction studies) groups, if appropriate.
    4. Determine surrogate or biochemical marker levels in human physiologic fluid specimens.
    5. Collate all information and prepare NDA for submission to regulatory agency.
  D. Phase 4 Studies
    1. Design phase 4 protocols for product extensions for new indications or improved delivery and obtain appropriate approval.
    2. Conduct randomized, double-blind, placebo-controlled studies in patients with new disease indication.
    3. Conduct bioequivalence or bioavailability comparison studies for novel formulation assessment.

VI. **Manufacturing (conducted concurrently with Nonclinical and Clinical Development)**
  A. Raw Materials
    1. Identify critical components, intermediates, and suppliers.
    2. Negotiate supply and certify vendors.
    3. Conduct site audit for selected vendors.
    4. Determine shelf life of raw materials.
  B. Scale-Up and Engineering
    1. Identify synthesis and formulation methods, including definition of equipment, processes, scale.
    2. Define processes and validate for fill, finish, and packaging.
    3. Determine procedure for waste disposal, including appropriate environmental assessments.
    4. Determine number of batches required to support development program and product launch.
  C. Documentation
    1. Generate table of contents for manufacture and control documents.
    2. Generate appropriate standard operating procedures.
    3. Develop validation protocols.
    4. Prepare regulatory documents, such as IND, yearly updates, and NDA.
    5. Conduct validation efforts, including preparation of progress reports.
  D. Drug Substance
    1. Define production time line for drug substance supplies for formulation development, stability, toxicology, and clinical studies.
    2. Determine characterization and specification requirements.

E. Stability
   1. Evaluate drug substance stability, including protocol preparation, approval, and study conduct.
   2. Evaluate drug product stability, including protocol preparation, approval, and study conduct.

F. Sterilization (if appropriate)
   1. Select and evaluate sterilization methods.
   2. Select dose levels and location for sterilization.
   3. Prepare sterilization protocol and obtain necessary approvals.
   4. Develop and validate Q.C. methods for sterilization.

G. Packaging and Labeling
   1. Identify each component in drug product.
   2. Define process for assemble and fill method.
   3. Generate labeling and package insert requirements.

2

Nonclinical Drug Development: Pharmacology, Drug Metabolism, and Toxicology

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I. INTRODUCTION

The discovery and development of a novel therapeutic agent, whether it is a small organic molecule or a macromolecule such as a protein and oligonucleotide, require scientific expertise for a number of different disciplines and an enormous amount of time and money. Whereas humans may be the ultimate test species to ascertain the safety and efficacy of a potential new agent, research studies in animal models are necessary to determine whether the drug candidate has a pharmacologic property that might mediate a human disease process and that it does not have a toxicity profile that could cause adverse events in humans at pharmacologic doses. Present estimates suggest that about 8–12 years and more than $300 million are needed to successfully discover and develop a novel therapeutic agent. Figure 1 presents the relationship between the dollars spent and time of development. It shows that the drug discovery and preclinical, or animal, phases are relatively inexpensive compared to the clinical and nonclinical phases of development.

Historically, for every 100 compounds screened for pharmacologic activity in animal models, only one has the necessary biological activity and safety for evaluation in humans. Of those compounds tested in humans, only 1 in 40 is successfully brought to the marketplace. This poor rate of success has been attributed to a number of factors, a primary one being that animals are not truly predictive of biological activity or safety in humans. The problem, however, may be that insufficient time and resources are put into characterizing a lead

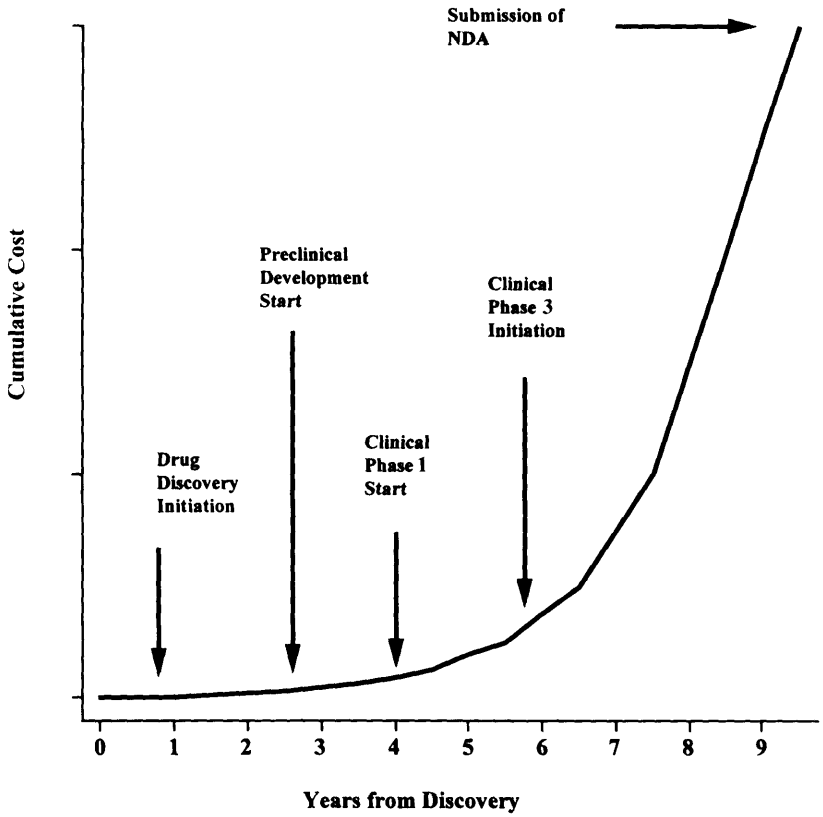

Figure 1. Time and cost profile for the discovery and development of a drug candidate.

candidate in pharmacology, drug metabolism, and toxicology animal models to first select the compound with the desired attributes for development, and then to critically evaluate the results from preclinical animal studies to ensure that a compound with developability problems does not enter into clinical studies until those problems are resolved. Instead of a rush from the first sign of biological activity in an in vitro pharmacology test to clinical evaluation, careful design, conduct, and interpretation of preclinical pharmacology and safety animal studies will detect "loser" candidates much earlier. This will allow precious time and resources to be devoted to finding development candidates with a better chance than 1 in 40 of successfully completing clinical studies and becoming a marketed therapeutic agent. Being able to identify the 3,999 losers of the 4,000 discovery leads that have a desirable biological activity as early as possible in the development process will save substantial time and resources.

This chapter describes the biological aspects of the nonclinical research programs of the drug development process. The chapter has been organized along the timeline for the nonclinical drug discovery and development process, with the major subsections being pharmacology or drug discovery, developability assessment, preclinical or pre-IND development, and nonclinical or post-IND development. The information presented should help drug development researchers to design experiments to evaluate lead candidates as they progress from drug discovery through the nonclinical studies of drug development.

II. OVERVIEW OF DRUG DISCOVERY AND DEVELOPMENT

Normally, the biological aspects of the drug discovery and development process can be subdivided into four distinct stages. The first is drug discovery, in which the pharmacology of a discovery lead is explored in appropriately characterized animal models, showing that the compound, or class of compounds, mediates a disease process and thus has potential human therapeutic benefit. This stage should also include preliminary studies to characterize the developability, which includes acute toxicity, preliminary pharmacokinetics, and initial formulation development, of a lead candidate or to select the optimal candidate from a group of compounds with similar pharmacologic properties (1,2). The second stage consists of preclinical development, in which the safety, including subchronic toxicology, pharmacokinetics, drug metabolism, and deliverability, of a drug candidate are studied in animal models. Additional pharmacology studies may also be conducted during this stage to optimize the route and frequency of administration, determine the pharmacological mechanism of action, and further explore the candidate's pharmacology profile for other possible disease indications. During the early (phase 1 and 2) clinical studies, the third stage of the process includes the initial human experiments to define the drug candidate's safety and tolerance and pharmacokinetics in normal volunteers and the candidate's efficacy in patients. In addition, the nonclinical research program is continued to extend the scientific database on the toxicity, metabolism, and delivery of the drug candidate. The final, fourth stage involves definitive safety and efficacy (phase 3) clinical studies in humans; carcinogenicity and reproductive toxicology studies in animals with supportive toxicokinetic experiments; and, where appropriate, human pharmacokinetic studies to evaluate potential changes in the extent and duration of delivery and disposition profiles caused by age, sex, race, interaction with other drugs, disease state, and hepatic and renal dysfunction. Figure 2 shows the interactions among these various biological stages. Each of these areas may also include a number of special experiments designed to confirm and extend results on a drug candidate's pharmacology and safety profiles.

III. PHARMACOLOGY

The drug discovery process has undergone enormous changes during the past few years. After years of first synthesizing individual compounds, then purifying and obtaining physical and chemical characterization of the new chemicals, and finally testing the NCEs in in vitro and in vivo pharmacology models of a particular human disease, the pharmaceutical and biotechnology industry has embraced combinatorial chemistry as a way to generate large numbers of organic compounds for evaluation. Combinatorial chemistry techniques include:

1. Having a large number of similar reactions taking place simultaneously in multiple-well reaction vessels, where the mixing of reagents and postreaction workup can be automated
2. Combining a mixture of reactants in the same reaction vessel to produce a library of products in a single vial and testing overlapping libraries to find those mixtures that contain active components
3. Using solid-phase chemistry, with the reactant attached to a support, and multistep syntheses, in which appropriate reagents are passed over the reactant on the support to prepare single or multiple products that are cleaved from the support and split and mixed so that subsequent steps have multiple starting materials

With these techniques, libraries have been created of many classes of NCEs some of which include peptides, peptoids, prostaglandins, imidazoles, alkaloids, heparins, oxazoles, benzodiazepines, and β-lactams.

The combinatorial chemistry-generated library is then screened for biological activity, usually in an in vitro system, in which a known biochemical process, which is thought to mimic a human disease, is agonized or antagonized. The increased number of compounds or mixtures of compounds to be tested has required pharmacologists to devise novel techniques to screen rapidly for biological activity. Because the amount of material available from combinatorial chemistry syntheses is small, miniaturization of the biological test system is a necessary first requirement. The large number of compounds makes automation of the tests the second requirement. The use of 96-well, and now 384-well or larger, titer plates and robotics to add the appropriate small amounts of combina-

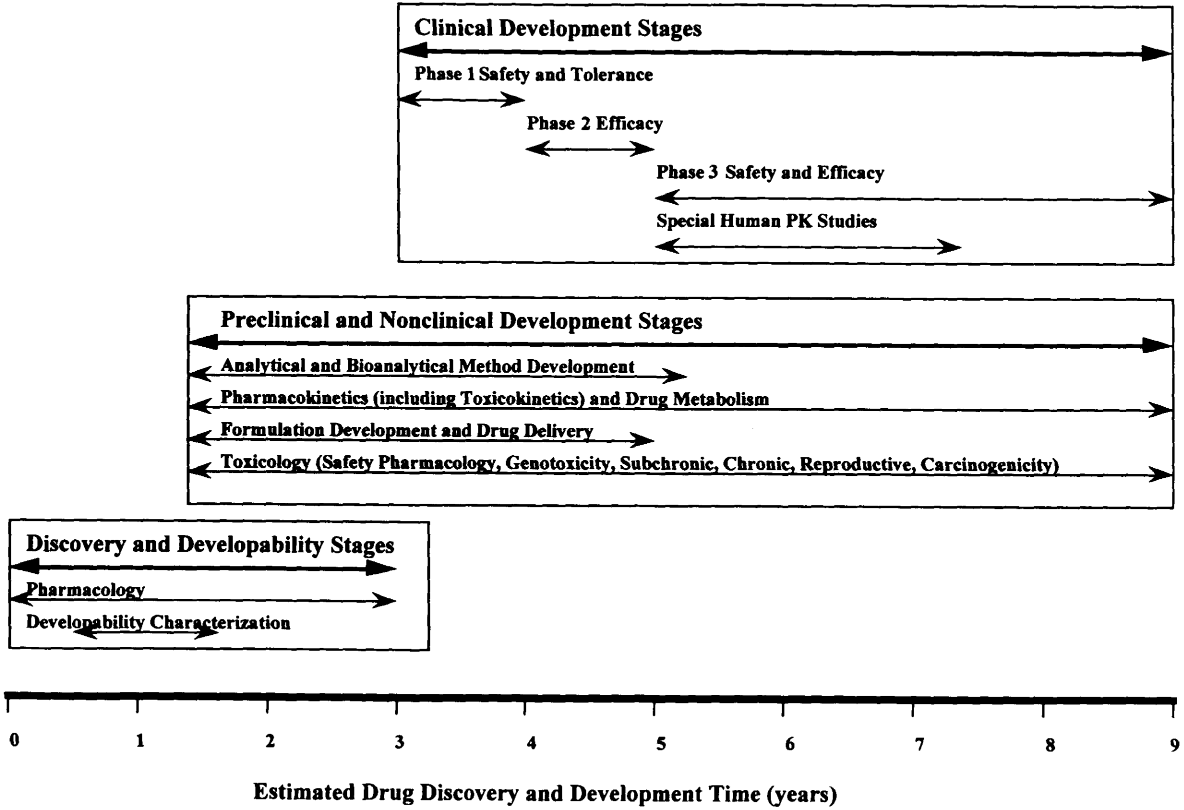
Clinical Development Stages
Phase 1 Safety and Tolerance
Phase 2 Efficacy
Phase 3 Safety and Efficacy
Special Human PK Studies
Preclinical and Nonclinical Development Stages
Analytical and Bioanalytical Method Development
Pharmacokinetics (including Toxicokinetics) and Drug Metabolism
Formulation Development and Drug Delivery
Toxicology (Safety Pharmacology, Genotoxicity, Subchronic, Chronic, Reproductive, Carcinogenicity)
Discovery and Developability Stages
Pharmacology
Developability Characterization
0
1
2
3
4
5
6
7
8
9
Estimated Drug Discovery and Development Time (years)

Figure 2. Interaction and timing of the various stages in the biological aspects of the drug discovery and development process.

torial chemistry libraries and reagents, including the material that generates the signal for a positive result, provides such a system for rapid assessment of biological activity. Those library vessels that elicit a positive or negative response, depending on the biological test being conducted, are identified, and the compound(s) of interest is isolated and identified.

After a sufficient quantity of the active compound discovered during the screening process has been synthesized, purified, identified, and characterized, additional studies are conducted to study the pharmacology of the lead. This more classic approach to evaluating the biological potency of a lead is referred to as SAR assessment. An important requirement in SAR determination is having or developing an animal model that correlates to, or mimics, a disease in humans. Developing these animal models can be time consuming and expensive and is often complicated by the fact that the model may not simulate the disease as manifested in humans. Many important human diseases, including psychoses, depression, Alzheimer's disease, and AIDS, do not yet have predictive animal models. After the animal model has been characterized, various dose levels of the lead(s), identified from screens of combinatorial chemistry libraries or other sources, are administered to the test species, and a dose-response curve is generated. The most commonly used endpoint is the dose that provides a 50% response (the ED_{50}). Structural analogues of the lead(s) can be synthesized and tested in the same model to generate a family of curves with varying biological potencies or ED_{50}s. The lead with the greatest biological activity is frequently selected for further development. However, at this point, many unanswered questions exist. Some of these are:

1. Does the animal model reflect, in all aspects, the disease in humans?
2. Is the delivery or extent of exposure of all the leads similar so that the generated dose-response curves accurately predict the compound with the greatest in vivo potency?
3. Are the route and frequency of administration and formulation used to dose the test species similar to those proposed for human evaluation?
4. Do the leads have similar pharmacokinetic and drug metabolism profiles so that the durations of exposure to the pharmacologically active compounds are similar?
5. Do any of the leads produce unacceptable toxicity in organs or physiologic systems not involved in the pharmacology of the compounds?

Before the formal preclinical development begins, attempts should be made to answer as many of these questions as possible. The following section discusses the drug developability experiments that can be conducted relatively quickly and cheaply to ascertain whether the lead(s) has the necessary biopharmaceutical characteristics for further development.

IV. DRUG DEVELOPABILITY ASSESSMENT

Completed drug discovery research studies indicate that a compound, or class of compounds, mediates a disease process and has potential as human therapeutic agent. Is this lead compound now ready to be transferred from the discovery area to a preclinical development group? Should additional, nondefinitive experiments be conducted to characterize more fully the properties of the lead candidate? If more studies are considered necessary, what experiments should be done?

This section describes some of the biological research experiments that could, and in most cases should, be conducted to evaluate the potential of a lead compound to become a developmental candidate. Figure 3 shows where these developability experiments fit into the drug discovery and development process. These nondefinitive developability studies may also uncover problems that have to be resolved before the definitive preclinical development studies required to support an IND submission are started and before the clinical protocols to evaluate the safety and efficacy of the drug candidate in humans are designed.

Before the definitive drug development program is begun, a number of questions should be asked and answered so that the research studies may be

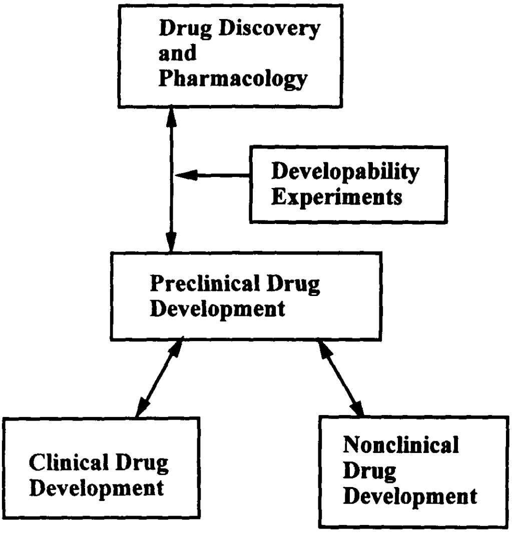
Drug Discovery and Pharmacology
Developability Experiments
Preclinical Drug Development
Clinical Drug Development
Nonclinical Drug Development

Figure 3. How drug developability experiments fit into the drug discovery and development process.

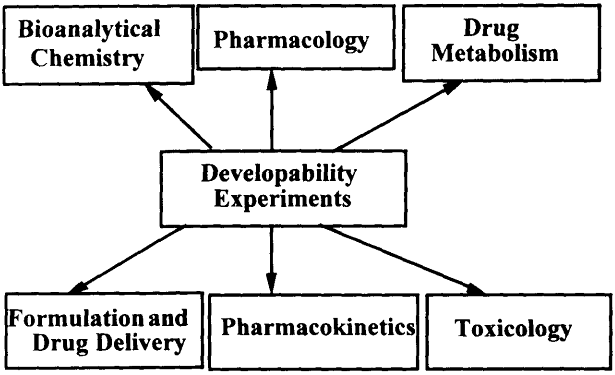

Figure 4. Scientific disciplines necessary for drug developability assessment.

planned effectively and the timelines for their completion can be determined. These questions include

1. What is the human disease indication for the candidate?
2. What is the proposed route and frequency of dosing for the candidate in human clinical studies?
3. What is the estimated candidate concentration in physiologic fluids and how long should that concentration be maintained so that the desired pharmacologic response could be obtained?
4. What, if any, are the biological markers to monitor toxicity or therapeutic effectiveness in nonclinical and clinical studies?
5. What definitive preclinical studies need to be completed before a human clinical program can be initiated?
6. What is the projected timeline for the completion of the preclinical studies and for filing the IND?

Additional questions need to be considered, including whether the drug candidate can be synthesized and purified in sufficient quantity to support a development program, how to document and validate these processes, how to characterize and document the impurities present in the drug substance and the drug product, and how to determine the stability of the drug substance and the drug product. However, those questions are outside the scope of this discussion.

Six scientific disciplines are involved in the developability characterization of a lead discovery candidate. As shown in Figure 4, these disciplines are in vivo pharmacology, bioanalytical method development, nonclinical formulation assessment, animal pharmacokinetics, drug metabolism, and toxicology. The following sections discuss each of these scientific disciplines in more detail.

A. Pharmacology

Preliminary pharmacology evaluations in in vitro or animal models will have shown that a lead candidate interacts with a biological process suggestive of human therapeutic benefit. Depending on the design and extent of these early studies, additional pharmacology studies may be needed to further characterize the dose, or physiologic fluid concentration, response curve using the proposed clinical route and frequency of administration. If possible, these pharmacology studies should be conducted in at least two species to show that the biological response is not species dependent. The ED_{50} dose should be determined, and that value, divided into the no-toxic-effect dose, described in the section on toxicology, calculates a therapeutic ratio or index. If the therapeutic ratio is one or less, a candidate will most likely elicit adverse events in addition to the beneficial response. Unless the candidate is for the treatment of a life-threatening disease, such as AIDS, cancer, or certain CNS indications, a low therapeutic ratio is a warning sign that the candidate may not have the necessary properties for further development. A therapeutic ratio of five or more indicates that a candidate will most likely produce a pharmacologic response before causing dose-limiting toxicity.

If possible, these developability pharmacology studies should be conducted with dosing to steady state unless the candidate is to be used as a single-dose therapeutic. The number of doses required to reach steady state depends on the compound's pharmacokinetic profile in the same animal model. These multiple-dose studies provide information on the frequency of dosing necessary to maximize the biological response. This is particularly important for compounds that inhibit an enzymatic system or are effective only during certain phases of a cell cycle.

These pharmacology evaluations assist in the selection of dose levels and route and frequency of administration for preliminary and definitive toxicology studies and for initial phase 1 safety and tolerance human studies. If the effective pharmacologic dose is unknown, underdosing and achieving no-therapeutic-response or overdosing and being unable to define a no-toxic-effect dose are undesirable possibilities. In such cases, the development of a potential beneficial therapeutic agent could be discontinued.

B. Bioanalytical Method Development

If not already available, a bioanalytical method needs to be defined and characterized for the quantification of the candidate in physiologic fluids. This method can then support experiments in each of the other scientific disciplines involved in assessing the developability of the lead candidate and, after appropriate validation, the preclinical, nonclinical, and clinical development of the drug candidate. For preliminary studies, a bioanalytical method should be characterized to demonstrate the range of reliable results, the lower and upper limits of quantification, specificity, accuracy, and precision. In addition, evaluations on the matrix to be used (blood, plasma, serum) should be conducted, and the stability of the candidate in each matrix should be determined.

The first step in characterizing a bioanalytical method is to select the analytical technique. For a candidate with a molecular weight of less than 2000, instrumental methods such as HPLC or GC with a variety of detectors, such as ultraviolet, fluorescence, flame ionization, electron capture, and mass spectrometry, may be used. A macromolecule (large peptide, protein, or oligonucleotide) may require an ELISA or RIA method. Samples in assay diluent and in a physiologic fluid and over a large concentration range should be analyzed to show that the technique produces an appropriate signal to detect the analyte and to determine the potential interference caused by the matrix. The ability to quantify a drug candidate in a physiologic fluid may depend on the matrix. For example, serum is a poor choice when the analyte interacts with clotting factors. The matrix that gives the best recovery and has the least interference when the drug candidate is added to whole blood should be selected.

The specificity of an assay evaluates the potential interferences from matrix components and from the different animal species to be used in pharmacology and toxicology experiments. Samples from each species to be studied are analyzed neat (with no added compound) and fortified with known amounts of the candidate, and the results are calculated by means of a standard curve prepared in assay diluent. The response obtained from the neat samples indicate the level of interference from each matrix, and the calculated amounts in the fortified samples show the difference in absolute recovery from the matrix compared with the candidate in buffer.

Acceptable results from the above experiments suggest whether a bioanalytical method should be able to quantify a drug candidate in a physiologic matrix. The range and reliability of quantification are assessed through the preparation and analysis of standard curves, prepared in either diluted or undiluted matrix, and multiple samples fortified at two or more concentrations. The standard curve responses that can be described by a mathematical equation (linear, quadratic, sigmoidal) define the range of reliable results. The lower limit of quantification is the lowest signal that can be accurately measured above background. The upper limit of quantification is the highest signal that can be defined by the response curve. The fortified samples provide information on precision, defined as the ability to obtain similar calculated concentrations from samples containing the same amounts of drug candidate, and accuracy, which is the ability to predict the actual concentration of the drug candidate in a sample.

The ability to measure a drug candidate in a physiologic fluid is not useful if the compound is unstable during collection, processing, storage, or sample preparation. Thus, a stability study should be conducted to ensure that the compound does not degrade in blood during processing to obtain plasma or serum, during the time (hours, days, and weeks) and under the conditions (room temperature, refrigerated, frozen at –20°C or –80°C) that specimens may be stored until analyzed, and during sample preparation. The design of stability experiments is usually compound specific. The results ensure that measured concentrations in unknown specimens reflect the amount of drug candidate present at the time of collection.

Successful completion of the above experiments will characterize methods for use in evaluating a lead candidate in animal models. If a candidate is selected for further development, the method will need to be validated (3,4) for each matrix and for each species before being used to support definitive toxicology, drug metabolism, and pharmacokinetic studies.

C. Early Nonclinical Formulation Development

Nonclinical formulation definition and the drug delivery characteristics of a lead candidate are not usually studied in detail during the transition from discovery to development. The experiments necessary to define an acceptable formulation depend on the proposed clinical route of administration. For a compound to be administered by I.V. injection or infusion, the formulation needs to be compatible with blood so that the compound does not precipitate when administered and has minimal local toxicity. Drug candidates that are highly lipophilic or have limited aqueous solubility are the most likely compounds to have these types of problems. A low extent of, or a high variability in, absorption can cause problems for drug candidates administered by other routes, such as oral, subcutaneous, and dermal. For candidates that are poorly absorbed, the amount reaching the site of action may be insufficient to elicit or to maintain a desired pharmacologic response. If the absorption is variable and the therapeutic ratio is low, a toxic response may be observed in some animals. Experiments conducted by the author have shown that when the extent of absorption is 50% or more and the variability of absorption is less than 50% of the amount absorbed, which gives a 25% to 75% range of absorption, the candidate should have acceptable bioavailability for further development. For candidates with an extent of absorption less than 25% of the administered dose or a variability of absorption of more than 100% of the amount absorbed, other formulations with absorption enhancers or solubilizers might be evaluated to improve the drug delivery profile. If improvement in the drug delivery profile is not possible, the chances that a drug candidate with low, variable absorption will become a therapeutic product are greatly reduced, and the candidacy of such a compound should be carefully considered.

An analytical method should be developed and validated for the quantification of a drug candidate in nonclinical formulations and should predict whether the compound degrades from the time of preparation to the time of dosing. A method with this ability is a stability-indicating assay. The physical and chemical properties of the candidate usually suggest a technique (heat, light, pH) that can degrade the compound. Samples stored under nondegrading and degrading conditions are assayed by the stability-indicating assay and, if possible, by another technique that can also determine if the original compound is present in the sample. If the candidate is not stable, formulation excipients possibly can be added to prevent the degradation, or the formulations can be maintained under conditions that provide sufficient stability for testing in animal models. However, when a candidate has limited stability in nonclinical formulations, the development of a clinical formulation with a sufficient shelf-life for marketing is problematic, and again the candidacy of such a compound should be carefully considered.

For proteins and other large molecules, degradation may include changes in the secondary or tertiary structure, provided that rearrangement back to original, biologically active structure does not occur. Stability-indicating assays for macromolecules should assess structural changes that cause reductions in biological activity. However, a protein may have a number of amino acids removed from one or both ends of the molecule and still retain some biological activity relative to the intact protein. This chemically modified peptide may have a different drug delivery profile or be more toxic than the parent protein. Structural modifications may not be apparent if biological activity alone is used to determine the amount of the macromolecule in a formulation. Thus, experiments to demonstrate that an assay method is stability-indicating need to be carefully designed and conducted. For macromolecules, a specific chemical assay, such as HPLC or ELISA, and a biological potency assay may be necessary to determine the concentration and stability of a compound in a formulation.

The stability-indicating assay should be used to determine the amount of drug candidate in nonclinical formulations used for dosing animals in preliminary pharmacokinetic, drug metabolism, and toxicology studies. For single-dose studies, samples from each formulation at each dose level can be collected before dosing and after the completion of dosing. For multiple-dose studies, samples from each formulation used can be collected before the first dose and after the last dose, or at selected other times. Results from these analyses ensure that the formulations contain the desired amount of the drug candidate, that the concentrations do not change during the dosing period, and that the animals are receiving the appropriate dose levels.

Without an acceptable nonclinical formulation, the extent and variability of delivery may make interpretation of results from developability studies meaningless and prevent the continued development of a potentially useful therapeutic agent.

D. Preliminary Animal Pharmacokinetics

The first animal pharmacokinetic study confirms that the bioanalytical method is useful in characterizing the absorption and disposition profiles of the candidate. The animal species for this study is usually the same as used in pharmacology evaluations, most likely a rodent. A study design for a candidate that has pharmacologic activity when administered P.O. to rats may consist of dosing two rats with I.V. bolus injections at a dose level between 25% and 50% of the pharmacologically active dose and dosing two rats P.O. at the pharmacologically active dose. Serial blood samples, collected from each rat and processed to obtained the desired physiologic fluid, are analyzed by means of the bioanalytical method. The plasma concentration versus time profiles after I.V. dosing provide preliminary information on the distribution and disposition kinetics of the candidate. These I.V. results certify that the bioanalytical method is useful for quantifying the candidate in specimens obtained from animals, predict the concentration range that can be expected in animal specimens, and assist in determining the sampling times to be used in more definitive animal pharmacokinetic experiments. The plasma concentration versus time profiles after P.O. dosing provide preliminary information on the absorption kinetics and the absolute bioavailability of the candidate. The design of additional animal pharmacokinetic studies depends on the results of the preliminary animal pharmacokinetic study, the theoretic kinetic profile needed to produce the desired pharmacology, and the results from preliminary toxicology experiments.

For most drug development programs, toxicology studies in two or more species are necessary. In this case, preliminary animal pharmacokinetic studies should be conducted in each species used in animal safety studies. If differences in delivery or disposition exist between species and result in an enhanced or decreased toxicology profile, the pharmacokinetics may explain, in part, the different toxicology profiles. If possible, physiologic fluid specimens should be obtained from animals in the preliminary toxicology studies to determine the extent and uniformity of exposure, which is termed toxicokinetics. Normally, three or four specimens from each animal are sufficient for toxicokinetic evaluations, but this level of sampling may not be possible for all studies. A single specimen at one collection time can be obtained from one or two animals in a dose group, and the other animals in that dose group can be sampled at other times. Analyses of these specimens provide data on the extent of exposure but not on the uniformity of exposure within a dose group. For multiple-dose studies, specimens are usually obtained after the first dose and after the last, or next to last, dose. The results provide information on possible changes in exposure and on the accumulation potential of the drug candidate and can be used to design multiple-dose animal pharmacokinetic and tissue distribution studies. If the change in disposition or accumulation is substantial, modification of the dosing regimen may be necessary to obtain the desired concentration profile after dosing to steady state.

E. Preliminary Drug Metabolism

The number and design of developability drug metabolism studies depend on the results from preliminary animal pharmacokinetic and toxicology studies. Drug metabolism evaluations determine distribution (where the compound goes), disposition (how long the compound stays), metabolism (whether the compound is changed and to what), and elimination (how the compound is removed) and are usually conducted with a radiolabeled compound. Early drug metabolism studies might be conducted with a less than desirable radiolabel, such as ^{125}I on a protein or ^{3}H at a potentially exchangeable site on an NCE. However, the results obtained from these studies can be misleading, reflecting the distribution and disposition of the label and not the drug candidate. For more reliable results, the radiolabeled compound should be radiochemically pure and stable and have a specific activity high enough to be measurable after dosing. Also, the label needs to be in a position where it does not affect the physical, chemical, or pharmacologic properties of the candidate and is not lost during phase 1 (oxidation, reduction, cleavage) or phase 2 (conjugation) metabolism.

If the candidate has a slow disposition phase, suggesting distribution into some extravascular tissues, or if the preliminary toxicology experiments identify potential organs of toxicity, a preliminary tissue distribution and mass balance study can be designed to evaluate the radioactivity level versus time profile in selected tissues, such as liver, kidney, fat (for a lipophilic candidate), muscle, skin, heart, and brain, and to determine the primary route(s) and rate(s) of elimination.

The total radioactivity minus the parent compound concentration (determined by the bioanalytical method) in a specimen estimates the amount of metabolites present. If the difference is minimal and does not change over time, the extent of metabolism is low. For plasma or serum specimens, a small difference indicates that metabolites are not present in systemic circulation. For bile or urine specimens, high levels of radioactivity suggest a primary route of elimination for the parent and metabolites. For a drug candidate cleared primarily by metabolism, a preliminary metabolite profile in urine and bile can determine the number of potential metabolites. When the level of a metabolite in a matrix is high, attempts to isolate and identify the metabolite can be undertaken. If sufficient quantities are obtained, the metabolite's pharmacologic and toxicologic activity potential can be evaluated, providing possible information on the pharmacologic and toxicologic mechanism of action for the candidate.

If metabolism in animal models is extensive or the generated metabolite(s) is shown to have toxic effects, in vitro metabolism studies using isolated P-450 isozymes, tissue homogenates containing the microsomal fraction, hepatocytes, and liver slices are commonly conducted to determine if the extent of metabolism and the metabolite profile is similar for animals and humans. The results from these in vitro metabolism comparison studies can be used to select the animal models for definitive development studies that have similar metabolism profiles to humans.

If the compound requires delivery to a particular site or organ to obtain the desired pharmacology, such as into the brain for CNS activity or into a tumor for an anticancer agent, preliminary drug metabolism studies can be conducted to demonstrate that the candidate is being delivered to the site of action and that the extent and duration of delivery are sufficient to provide the desired pharmacology.

F. Acute Toxicology Studies

Toxicology studies are conducted to define the safety profile of a candidate and include definition of the no-toxic-effect dose, MTD, potential organs of toxicity, and potential biochemical markers to detect and track toxic events. Most developmental compounds that do not become therapeutic products have unacceptable toxicity in animals or humans. Before the definitive toxicology studies needed to support an IND submission are initiated, a number of animal experiments can be conducted to characterize the potential toxicity of the candidate. These early toxicology evaluations are usually conducted in the same species as used in pharmacology evaluations. As mentioned earlier, the lowest dose that has no toxicity or an acceptable level of toxicity is compared with the dose that gives the desired pharmacologic response in the same animal species to obtain a therapeutic ratio or index for that species.

A toxicology program to obtain toxicologic characterization of a discovery lead should be accomplished through close interaction with the efforts of other scientists conducting developability experiments. Before drug safety studies are conducted, a sufficient quantity of drug candidate should be available and characterized so that testing is conducted with a known compound. If the candidate requires formulation before dosing, the formulation should be the same for each study. If a change in the synthesis, purification, or formulation is necessary to improve the biopharmaceutical properties of the candidate or the drug delivery profile, then some of the early toxicology studies should be repeated with the new formulation to determine whether the safety profile has been altered. These early studies do not need to be, but in many cases are, conducted according to

GLP requirements. However, they should be designed and conducted as close as possible to the processes used for definitive GLP toxicology studies. Then, the results will be scientifically defensible and useful in predicting the toxicity expected from the GLP studies. Examples of the early toxicology studies needed to characterize a candidate include the following:

1. *Acute Single-Dose Tolerability Studies*

To evaluate the qualitative and quantitative single-dose toxicity of a drug candidate, a single dose at a number of dose levels is administered by the proposed clinical route, and the animals are observed for 14 days after dosing. The acute study is not an LD_{50} study, which is not needed for overall risk assessment according to an ICH guideline (5). This ICH Guideline suggests that the drug candidate dose levels include at least one that produces pharmacologic activity and one that causes overt evidence of major or life-threatening toxicity, and that a vehicle control group be included. The acute toxicity study should evaluate both the I.V. route and the intended clinical route of administration, unless the clinical route is I.V. The studies should be conducted in two relevant mammalian species, rodent and nonrodent, and unless scientifically unjustifiable, should use equal numbers of males and females for each species evaluated. The test species is observed for 14 days after dosing and, as with all toxicology studies, all signs of toxicity with time of onset, duration of symptoms, and reversibility are recorded. Also, the time to first observations of lethality is recorded. Gross necropsies are performed on all animals sacrificed moribund, found dead, or terminated after 14 days of observation, and the results are presented by group. An evaluation of results should include all observations made and a discussion of the toxicologic findings and their implications to humans, taking into account the pharmacology of the drug candidate, the proposed human therapeutic use and dose, and experience with related drugs. The highest no-toxic-effect dose and the highest nonlethal dose are noted.

2. *Dose-Range-Finding Studies*

The doses for definitive toxicology studies are defined in dose-range-finding studies. These usually include four dose levels, with the highest level being the dose that did not cause acute toxicity, and a vehicle control group, and they are conducted in each species proposed for use in definitive toxicology studies. For rodents, dose groups usually have 6 to 10 animals, 3 to 5 animals per sex. For nonrodent species, normally beagle dogs or nonhuman primates, the number of animals in each dose group is commonly 4, 2 animals per sex. Endpoints for dose-range-finding studies may include, but are not limited to, weight loss, activity changes, clinical chemistry changes, and histology and pathology evaluations at necropsy. The primary goal of these studies is to determine an MTD.

The route of administration and the frequency and duration of dosing are determined from the expected clinical use of the candidate.

3. *Pilot, 14-Day Studies*

A dose level that causes toxic changes, such as morbidity or salivation, and one that produces the no-toxic-effect are determined during 14-day studies. For a drug candidate to be used for a non–life-threatening clinical indication, at least two animal species are tested, one rodent and one nonrodent. The information gained by these studies is used to model the definitive GLP toxicology studies so that these experiments are conducted with a cost-efficient design and are data productive. These early toxicology studies can also evaluate the potential for antibody production, if the candidate might be antigenic, and clinical chemistry changes in physiologic parameters (electrolyte or biochemical imbalances, changes in liver enzymes). These data identify potential biological markers that can be used in definitive toxicology and clinical studies to evaluate and possibly predict adverse events.

Organs that are the targets of toxicity may be identified during the above toxicology studies by a full histology workup of animals in each dose group and from the results obtained from the analyses of clinical chemistry samples (discussed in more detail in the preclinical toxicology section). The level of the drug candidate in the identified target organs of toxicity can be determined by the drug metabolism group in an attempt to correlate the observed toxicity with high or accumulated concentrations of the candidate, providing toxicodynamic correlation. If possible, investigations into the biochemical mechanism of identified toxicity should be initiated. Results from these experiments can provide insight into potential toxicities in definitive toxicology studies, identify biological markers that predict a toxic event, and suggest conditions in patients where administration of the drug candidate is contraindicated. If results from the early toxicology studies show that a candidate has an unacceptable level of toxicity, the development candidacy of such a compound should be carefully considered.

G. Drug Development Candidate Selection

Many lead discovery candidates are transferred to the preclinical development process with insufficient characterization to assess their development potential. This lack of knowledge usually results in poorly designed experiments that are not data productive and that, in many cases, have to be repeated when a candidate shows unexpected toxicity, low and variable delivery, instability in formulation, or unacceptable pharmacokinetic and drug metabolism profiles. In all too many cases, the recognition of these problem areas results in termination of development for a potentially useful therapeutic agent. At best, the problems encountered cause a delay, at times substantial, in the development of a candidate while additional studies are conducted to elucidate the causes of the problems and minimize their effect. Then, the definitive development experiments have to be repeated.

The developability experiments in six scientific disciplines shown in Figure 4 more fully characterize a lead discovery candidate before the compound enters the definitive preclinical, then the nonclinical and clinical drug development processes. The experimental designs could also be used, with minor modifications, to evaluate a class of compounds and thus to select the candidate with the best characteristics for further development. With appropriate planning and commitment of resources, these studies can usually be completed in 3 to 6 months if major problems are not encountered in one or more of the scientific areas.

If these developability experiments are completed as part of the transition from discovery to development, candidates that do not have the characteristics necessary to become therapeutic agents can be identified early and prevented from entering the development process. Analogues of a compound with unacceptable characteristics can be evaluated to find a development candidate that has more optimal properties. In addition, the results from the developability studies will allow the preclinical development studies to be designed and conducted in a timely, cost-efficient manner and thus allow the candidate to have an earlier entry into the clinic.

V. PRECLINICAL DRUG DEVELOPMENT

Before entering into a clinical evaluation program, a drug candidate is subjected to a number of preclinical studies to further define and characterize its safety profile. The results from the pharmacology, developability, and preclinical studies are documented in technical reports or scientific publications and used to prepare the IND submission. All of the preclinical studies, described in the section below, and nonclinical studies, discussed in the following section, need to be conducted according to GLP regulations.

A. Good Laboratory Practice

Research studies intended for submission to a regulatory agency are to be conducted according to GLP regulations, as published by regulatory authorities in all the leading pharmaceutical markets, such as the United States (the FDA regulations applicable to GLPs are provided in Title 21 Code of Federal Regulations, Part 58), European Community, and Japan. Good Laboratory Practice regulations are very similar worldwide; however, researchers are cautioned to review the regulations for the marketing area to ensure that the completed studies are in compliance.

Good Laboratory Practice regulations concern standard methods, facilities, and controls used in conducting nonclinical laboratory studies and are used to assure the quality and integrity of generated data. The standards relate to both the design and the conduct of the research studies and the qualifications of the personnel and facilities involved with all aspects of the experiments. The GLPs necessitate that SOPs be written for all routine or standard procedures in the laboratory, that all personnel involved with the studies be sufficiently trained and experienced to perform their assigned functions, that an adequate number of personnel be available to conduct the study, that the facilities be appropriately designed and maintained, and that a group, commonly called QA, monitor and check the results from the studies to ensure that the experiments are conducted in compliance with the regulations.

B. Bioanalytical Chemistry

The bioanalytical method, defined and characterized during developability assessment, can be used to support definitive pharmacokinetic and toxicology studies after the assay has been appropriately validated for each physiologic matrix and each species to be evaluated. The validation experiments need to address and define acceptance and rejection criteria for the range of reliable results, the lower limit (and if appropriate as for an ELISA or RIA method, the upper limit) of quantification, accuracy, precision, specificity, and recovery and should include appropriate stability studies. These stability studies will ensure that the analyte is stable in the physiologic matrix from the time of collection to the time of analysis. Guidelines for validation of a bioanalytical method have been published (3,4). ICH guidelines (6,7) have been issued for validation of analytical procedures and can be used for guidance for validation of bioanalytical methods. The validated method should be documented in a test assay procedure and supported by appropriate SOPs. Also, the results from the validation experiments should be documented in a technical report and included in the IND submission.

C. Pharmacokinetic and Bioavailability Experiments

Pharmacokinetic and bioavailability (absolute and relative) experiments are usually designed and conducted to evaluate dose proportionality over the dose range used, or expected to be used, in toxicology studies and possible species-to-species differences in pharmacokinetic profiles. With the incorporation of one or two I.V. dose levels into the study protocol, the drug candidate's absolute bioavailability can also be determined, and information on the linearity of absorption, distribution, and disposition kinetics can be obtained. If more than one drug formulation is to be used in toxicology studies (e.g., an oral solution for rodent studies and tablets or drug in capsules for dosing the larger, nonrodent species), relative bioavailability experiments comparing the formulations can determine if the extent of delivery is similar or different and thus can make extrapolation of pharmacology and toxicity results between animal species meaningful and useful in designing the later nonclinical studies and phase 1 safety and tolerance studies in humans.

D. Drug Metabolism

Drug metabolism experiments in animal species used or to be used in toxicology studies are designed and conducted to evaluate the mass balance and tissue distribution by use of an appropriately labeled compound, usually a radioactive isotope such as carbon-14. Before animals are dosed, the radiochemical purity needs to be evaluated, and the stability in physiologic matrices must be studied. If the radiolabel is nonmetabolically removed from the compound, the results from the drug metabolism experiments or other studies using the labeled compound will have little, if any, meaning or usefulness in the determination of the metabolic fate of the drug candidate.

One of the first studies conducted should be protein binding in animal and human physiologic fluid. The pharmacologic and toxicologic activity of a drug candidate is usually attributed to the free or unbound fraction in systemic circulation and not to the total drug content, which includes both free and bound drug. The unbound drug is the species that passes through the cell walls of blood vessels and is distributed to various organs, including the pharmacologic and toxicologic sites of actions. The free and bound fractions of a drug candidate are in equilibrium so that as the free drug is removed from systemic circulation, the bound drug disassociates to maintain the free-to-bound ratio. A drug candidate that is highly and tightly bound, e.g., more than 95%, to blood proteins may not have sufficient distribution to attain the necessary concentration at the site of action to elicit a pharmacologic effect. If this is the case, a bioanalytical method that quantifies unbound drug may be needed, and the pharmacokinetic profile of the free fraction can be evaluated. For a drug with a protein binding of less than 95%, the amount of free drug and the equilibrium process generally provide a good correlation between total drug concentration in systemic circulation and pharmacologic or toxicologic responses.

The two most common drug metabolism studies are mass balance and tissue distribution. Mass balance studies are usually conducted in both the rodent and the nonrodent species used for toxicology evaluations, whereas tissue distribution is performed only in the rodent. For mass balance, a radiolabeled compound is administered to the test species, and urine, feces, and, if necessary, expired air are collected at intervals and counted for total radioactivity. Commonly used intervals are 0–4, 4–8, 8–12, 12–24, and then daily, up to 168 hours or until more than 95% of the administered dose has been excreted. Depending on the pharmacokinetic profile of the candidate, other collection intervals can be selected to give a better picture of the excretion profile. For tissue distribution, a radiolabeled compound is administered to the test species, and after predefined times, usually 2, 4, 8, 24, and 48 hours, the test species is sacrificed, and tissues are collected, processed, and counted for total radioactivity. The tissues commonly evaluated are similar to those collected during necropsy in toxicology studies (listed in Table 1) plus the carcass. A routine aspect of most tissue distribution studies is whole body autoradiography (WBA). Recent advances in WBA allow this technique to quantify the amount of the radioactivity in tissues.

Table 1 Tissues Collected at Necropsy and Prepared for Histopathologic Evaluation

Tissue	Tissue
Adrenal glands	Pancreas
Aorta	Pituitary gland
Bone marrow (sternum)	Prostate gland (males)
Brain (usually at least three levels)	Rectum
Cervix/Vagina (females)	Salivary gland (mandibular)
Epididymides (males)	Sciatic nerve
Esophagus	Skeletal muscle
Eyes with optic nerve	Skin from the abdomen
Femur with articular surface	Spinal cord (usually at least three levels)
Gallbladder	Spleen
Heart	Thymus
Large intestine (including cecum and colon)	Thyroid and parathyroid (when in same section)
Testes (males)	Tongue
Small intestine (including duodenum, jejunum, and ileum)	Stomach (including cardia, fundus, and pylorus)
Kidneys	Trachea
Liver	Uterus (females)
Lungs with bronchi	Urinary bladder
Lymph nodes	Gross lesions
Lacrimal gland	Seminal vessels (males)
Mammary gland (females)	Vertebra
Ovaries (females)	Injection site (if appropriate)

Some researchers think that WBA should replace the classic tissue distribution study to profile the organs and systems that are exposed and may accumulate the drug candidate and its metabolites.

These preclinical drug metabolism studies may also include metabolite profiling in plasma, selected tissues, urine, and bile to assess the distribution and disposition of potentially important metabolites, such as those having a level 5% or greater relative to the parent compound. Metabolite profiling requires a technique to separate the parent compound from metabolites and other endogenous compounds. For small molecules, HPLC is usually the method of choice. For macromolecules, gel or capillary electrophoresis techniques can be defined with sufficient resolution capability to separate the compounds. Those metabolites representing more than 5% of the parent compound are usually identified with such techniques as mass spectrometry and nuclear magnetic spectroscopy. After identification, those metabolites that might elicit a pharmacologic or toxicologic response can be synthesized and tested in appropriate animal models. Many novel drugs have been discovered during metabolite characterization of drug candidates. These new compounds usually have attributes, such as better extent of delivery, longer or shorter disposition kinetics, less potential for accumulation, or better clearance properties, that make them better drug candidates than the parent compound.

E. Toxicology

Before human clinical trials are initiated, a number of toxicology studies need to be completed and documented in the IND submission. In addition to the studies listed above for toxicology developability assessment, preclinical toxicology studies include local tolerance, genotoxicity, safety pharmacology, and subchronic tests.

One of the most troublesome aspects in interpretation of toxicology results is determining whether these data are predictive of toxicity in humans. Often, animal toxicology may not correlate with human safety because the observed adverse effects are species specific. For example, HMG-CoA reductase inhibitors induce cataracts, potentially a drug-candidate-killing effect, in beagle dogs but not in rats or monkeys. Human clinical use of these therapeutic agents also has not shown this adverse event, suggesting that the beagle is susceptible to this problem but other species are not. Species specificity is sometimes discovered early in the development of a drug candidate, such as the drug developability phase discussed earlier, and can be used to design the early human trials to ascertain if humans also manifest the observed toxicity.

1. Local Tolerance

An ICH Guideline (8) indicates that local tolerance evaluations are to be conducted in animals by use of the route of administration proposed for human clinical testing and that these evaluations are to be performed before human exposure. The assessment of local tolerance may be part of other toxicity studies.

2. *Genotoxicity*

Registration for marketing of pharmaceuticals requires an assessment of the drug candidate's genotoxic potential. Two ICH Guidelines (9,10) have been issued for genotoxic testing, which includes in vitro and in vivo studies that are designed to determine if a compound induces genetic damage either directly or indirectly and by any of a number of mechanisms. Positive genotoxic compounds have the potential of being human carcinogens or mutagens, that is, these drug candidates may induce cancer or heritable defects.

Three tests are recommended to evaluate the genotoxicity potential of a drug candidate: (a) a test for gene mutation in bacteria (the Ames test), (b) an in vitro cytogenetic evaluation of chromosomal damage by use of mammalian cells such as human lymphoblastoid TK6, CHO, V79, and AS52 cells or an in vitro mouse lymphoma L5178Y cell line tk assay, and (c) an in vivo study for chromosomal damage by use of rodent hematopoietic cells. Drug candidates that give negative results in these three tests are usually considered to have demonstrated an absence of genotoxic activity. Depending on the proposed therapeutic use, positive compounds may need to be tested more extensively.

3. *Safety Pharmacology*

Safety pharmacology involves assessing the effects of a drug candidate for pharmacologic activity on the functions of organ systems other than the target system. Normally the organ systems that are evaluated are the cardiovascular, central nervous, renal, and respiratory systems. Depending on the physical and chemical characteristics of the candidate and the route of administration, another system could be the gastrointestinal system. Safety pharmacology studies need to be conducted (8) before human exposure and may be additions to other toxicology studies or separate studies.

4. *Subchronic Toxicology*

The FDA and most other regulatory agencies require subchronic toxicity studies in two species, one of which is a nonrodent, before human clinical trials are initiated. The recommended duration of the subchronic toxicity studies is related to duration of the proposed clinical trials. An ICH Guideline (8) suggests the minimum duration of toxicity studies, shown in Table 2, needed to support phase 1, 2, and 3 clinical trials in which humans are to be exposed to the drug candidate for varying durations.

Table 2 Duration of Multiple Dose Toxicology Studies Needed to Support Phase 1, 2, and 3 Clinical Trials

	Minimum Duration of Toxicity Study	
Duration of Clinical Trial	Rodents	Nonrodents
Single dose	2–4 weeks*	2 weeks
Up to 2 weeks	2–4 weeks*	2 weeks
Up to 1 month	1 month	1 month
Up to 3 months	3 months	3 months
Up to 6 months	6 months	6 months
Greater than 6 months	6 months	chronic

*In Europe and the United States, 2-week studies are the minimum duration. In Japan, 2-week nonrodent and 4-week studies are needed. *Note:* Support for phase 3 clinical trials in Europe and for marketing in all regions required longer minimum duration toxicology studies than listed in the table.

The two most common species used in subchronic toxicology studies are the rat and the dog. The most common strain of rat used within the pharmaceutical and biotechnology industries is the Charles River CD rat, which is Sprague-Dawley derived and an outbred strain. Some companies use the Fisher 244 albino rat, which is an inbred strain, because it does not grow as large as the Charles River CD rat. Other rodent species sometimes used for subchronic toxicity include the mouse and the hamster. The beagle dog, purebred and specifically bred for research, is the most common nonrodent species used in toxicology. Cynomolgus and rhesus monkeys are also used as the nonrodent toxicology species, primarily by the biotechnology industry developing macromolecule therapeutics but also more and more frequently by pharmaceutical firms evaluating NCEs. The rabbit, which is commonly one of the species used in reproduction toxicology evaluations, has also been used as the nonrodent species for subchronic testing.

During the past few years, significant advances have been made for effective dosing regimens of animals in toxicology studies. The most common route of administration for human therapy is oral, usually as tablets or capsules. Other routes include I.V., pulmonary, dermal S.C., intramuscular, and buccal. Whatever the proposed route of administration for humans, the preclinical animal toxicology studies should use the same route of delivery. For rodents, oral dosing of tablets or capsules is not possible, but daily, or more frequent, oral gavage is a now standard technique. For larger species, the tablets or capsules can be placed in soft gelatin capsules and dosed. Present-day technology allows continuous infusion of both rodent and nonrodent species for evaluation of drug candidates to be administered as I.V. infusions.

Whenever possible, the proposed clinical formulation should be used in preclinical toxicology evaluations, because formulation excipients can be important in the extent and duration of delivery and in local tolerance. For oral dosing to rodents, the solid clinical formulation can be ground and the appropriate amount dissolved or suspended in water prior to gavaging. The most common dosing volume is 10 ml/kg, but other volumes can be used. The volume administered should be uniform for all dose groups, including the vehicle control group.

For rodent subchronic studies, 10 to 25 animals/sex/group are used, with the smaller groups used for shorter (2–4 week) studies and the larger groups for longer-term (more than 13 weeks) studies. If an interim sacrifice or a reversibility phase, which is a drug-free recovery phase, is incorporated into the study design, an extra 10 animals/sex are commonly added to each dose group, including the vehicle control group. For nonrodent subchronic studies, the number of animals/sex/group is usually three to six, depending on the length of the study and the expected toxicology profile.

Dose selection for subchronic and chronic toxicology studies should be based on the results from acute toxicity studies and pharmacokinetic evaluations. The three typical dose levels are (a) a no-toxic-effect level, which should be at least equivalent to, and hopefully a multiple of, the proposed human dose, (b) a dose level that produces a toxic effect in clinical observations, clinical pathology, or histopathologic changes, and (c) a dose level between these two.

5. Formulation Analyses

Analyses of formulations for a drug candidate content are conducted to ensure that doses administered to animals in toxicology, pharmacokinetic, and drug metabolism studies have the proper level of the drug candidate. Before these analyses are performed, a stability-indicating analytical method that can quantify the drug candidate in the formulation needs to be defined and validated (6,7) for sensitivity, linearity, precision, accuracy, and robustness. If the dosing formulation is changed between studies, revalidation of the analytical method for application to the new formulation is necessary.

For acute toxicity, single-dose pharmacokinetic, and single-dose drug metabolism studies, formulations for each dose level, including the vehicle control, are commonly analyzed before and after administration. If no apparent change in the drug candidate content is detected, the animals are assured to have been dosed with the appropriate amount of the compound. For subchronic and chronic studies, including carcinogenicity studies, and multiple-dose pharmacokinetic and drug metabolism experiments, formulations for each dose level are analyzed for drug candidate content before the first dose, at predefined times during the course of the study, and after the last dose. If the length of study requires that the formulations be prepared periodically, content analyses need to be performed on some of the new formulations to ensure that the method of preparation provides a uniform candidate content. If the drug content in a formulation drops below a predefined acceptance criteria, that formulation should not be used for dosing animals.

6. Toxicokinetics

For many years, the dose levels of a drug candidate administered to the test species in the various dose groups of a toxicology study were used to correlate the observed toxic effects with the drug candidate and to show that the effects increased with increasing dose. The administered dose levels were assumed to predict, and be proportional to, the amount of drug candidate that was in the body. However, for drug candidates that are poorly absorbed, have variable absorption, or show saturable absorption as the dose level increases, the administered dose has been shown not to be a uniform predictor of toxicity. Ensuring that test species have an increased exposure to the drug candidate as the dose levels increase has become a critical aspect of toxicology studies. Equally important is that the extent and duration of exposure are not changed after multiple-dose administration. An ICH guideline (11) has been issued on the generation of toxicokinetic data to support the development of a drug candidate. The objectives of toxicokinetics include:

1. Describing the systemic exposure in each of the test species used in toxicology studies and showing how exposure relates to dose level and the time course of the study
2. Correlating the extent of exposure with toxicologic findings and contributing to the assessment of these findings to clinical safety
3. Supporting the choice of test species and treatment regimen for nonclinical toxicology studies
4. Along with toxicity results, providing information on the appropriate design for subsequent nonclinical toxicity studies and human clinical studies

Toxicokinetic data, considered an integral part of a nonclinical program, can be obtained from the test species in a toxicology study or in specially designed supportive studies. The primary focus of toxicokinetic data is to assist in the interpretation of toxicity results and not on characterizing the basic pharmacokinetic parameters of the drug candidate being studied. Not all toxicology studies need to include a toxicokinetic component. If the extent and duration of exposure of a drug candidate in a particular formulation for a given test species has been generated for the dose level range to be used in a toxicity study, additional toxicokinetic evaluations are not generally necessary. Toxicology studies, which are usefully supported by toxicokinetics, include single-dose studies for which results from preliminary pharmacokinetic studies may be applicable; multiple-dose studies in which toxicokinetic data may predict whether multiple-dose pharmacokinetic studies are necessary; reproductive studies, which may use different test species that have an altered absorption and disposition profile due to pregnancy; and carcinogenicity studies, in which the test species may be dosed differently for other toxicology studies and changes in exposure can occur because of age.

7. Hematology, Clinical Chemistry, and Histopathology

Three important aspects for detecting and understanding the adverse events observed during a toxicology study are hematology and clinical chemistry assays and histopathology evaluation of tissues collected at necropsy. Hematology parameters commonly evaluated include those listed in Table 3. These parameters should be determined periodically during the toxicity study, with the number of evaluations depending on the length of the study. Clinical chemistries routinely determined include those listed in Table 4. Urinalysis also may be performed but is usually limited to nonrodents and should include microscopical examination of sediment. Pretreatment clinical chemistry analyses and the number of determinations per group should be the same as for hematology. Depending on the pharmacology and toxicology profile of a drug candidate, other biological marker analyses can be included in hematology and clinical chemistry evaluations. Results from these additional tests can provide information on physiologic parameter changes caused by the drug candidate in animal models and may

Table 3 Hematology Parameters Evaluated During Toxicology Studies

Parameter	Abbreviation
White blood cell count	WBC
Red blood cell count	RBC
Hemoglobin concentration	HGB
Hematocrit	HCT
Mean corpuscular volume	MCV
Mean corpuscular hemoglobin concentration	MCH
Mean corpuscular hemoglobin	MCHC
Platelet count	PLT
Prothrombin time	PT
Activated partial thromboplastin time	APTT

Table 4 Clinical Chemistry Parameters Evaluated During Toxicology Studies

Parameter	Abbreviation
Total protein	TP
Triglycerides	TRI
Albumin	A
Globulin	G
Albumin/Globulin ratio	A/G
Glucose	GLU
Cholesterol	CHOL
Total bilirubin	TBILI
Blood urea nitrogen	BUN
Creatinine	CREAT
Creatine phosphokinase	CPK
Alanine ainotransferase	ALT
Aspartate aminotransferase	AST
Alkaline phosphatase	ALK
Gamma-glutamyltransferase	GGT
Lactate dehydrogenase	LDH
Calcium	Ca
Phosphorus	Phos
Sodium	Na
Potassium	K
Chloride	Cl

be used to evaluate pharmacologic and toxicologic events during human clinical studies.

Tissues collected at necropsy and prepared for histopathologic evaluation include those previously listed in Table 1. Routine sectioning and examination are recommended for all tissues from rodent and nonrodent animals used in subchronic and chronic studies. Requirements for special histopathology examination depend on adverse effects that are indicated by in-life clinical pathology changes and are usually on a case-by-case basis. Electron microscopy (EM) is a useful extension of light microscopic evaluation in determining morphologic alteration of cellular structures not otherwise clearly visualized. Selected specimens can be processed for EM examination when it is justified. The application of EM to all tissues is considered impractical and unnecessary.

8. Immunogenicity

Many proteins, polypeptides, oligonucleotides, and other large molecules are immunogenic in the animal models used in pharmacology and toxicology evaluations. According to an ICH Guideline (12), the potential for antibody formation should be determined during the conduct of subchronic toxicology studies to aid in the interpretation of results from these and later studies. Antibodies that are formed are characterized as to titer, number of responding animals, neutralizing or nonneutralizing, change in pharmacologic or toxicologic response, complement activation, and immune complex formation and deposition. If the observed immune response neutralizes the pharmacologic or toxicologic effects of the drug candidate, modification of the study design may be warranted. Because the induction of antibody formation in animal models is not predictive of a similar response in humans, no special significance to animal antibody formation should be ascribed unless the interpretation of results from pharmacology or safety studies is compromised. However, if antibodies are formed during animal studies, the potential for antibody formation in humans should be assessed during early clinical development to ensure that antibodies will not adversely affect the pharmacologic profile and do not increase the toxicity of the drug candidate in humans.

VI. NONCLINICAL DRUG DEVELOPMENT

After a drug candidate enters into human clinical testing, information on the pharmacokinetics and toxicology of the compound in the relevant species finally becomes available. The results from pharmacology, developability, and preclinical drug development experiments should be re-evaluated in light of this new information to ascertain if the animal models were predictive of the efficacy and safety in humans. If the animal results are extrapolative to humans, the remaining nonclinical animal studies are fairly straightforward and are conducted to provide supportive information on the safety of the drug candidate. However, if the early animal data do not extrapolate to the human situation, additional animal experiments should be designed and conducted to better and more fully understand the observed pharmacology and toxicology in humans. Considering the expense in both time and money to conduct nonclinical drug development studies, most pharmaceutical and biotechnology companies meet with the appropriate regulatory agencies to discuss the study designs and protocols and how dose levels were selected to avoid nonacceptance of regulatory submissions later on.

A. Pharmacokinetics

Unless justified from pharmacokinetic results from humans, additional animal pharmacokinetic are not usually conducted during nonclinical development. Types of animal pharmacokinetics that might be performed include: (a) multiple-dose pharmacokinetics to assess accumulation or changes in clearance caused by enzyme induction or inhibition, (b) bioavailability comparison when the formulation used in early toxicology studies is changed to alter the delivery profile of the drug candidate, (c) drug candidate metabolite distribution and disposition evaluations, (d) effect of food and time of feeding on the extent and duration of absorption, and (e) drug-drug interaction if the animal model is considered predictive of humans.

B. Drug Metabolism

After initiation of human clinical studies, drug metabolism studies are continued to build the database to show that the results from the animal models used to demonstrate the pharmacology and toxicology of the drug candidate can be extrapolated to the human situation. The most common drug metabolism studies conducted during nonclinical drug development are multiple-dose tissue distribution, additional characterization and evaluation of metabolites, and studies such as fetal-placental transfer and lacteal secretion, which are designed to support reproductive toxicology evaluations.

Although most regulatory agencies agree that a single-dose tissue distribution study in rodents is needed to support the development of a drug candidate, and that this study often provides sufficient data on the distribution of the compound, a multiple-dose tissue distribution study may yield additional information (13). This study, for which no consistent requirement currently exists, may be appropriate when: (a) the apparent half-life of the drug candidate or a metabolite in organs or tissues significantly exceeds the apparent terminal disposition half-life in plasma and is more than twice the dosing interval in toxicity studies, (b) when the steady-state concentrations of the drug candidate or a metabolite in systemic circulation, usually first detected from toxicokinetic results from multiple-dose toxicology studies, are substantially higher than predicted from single-dose pharmacokinetic studies, (c) when the drug candidate is being developed for site-specific targeted delivery, and (d) when histopathology changes that were not predicted from shorter-term toxicology studies, single-dose tissue distribution studies, or pharmacology studies are observed. The study design for multiple-dose tissue distribution studies is usually compound and result specific and thus is determined on a case-by-case basis.

Reproductive toxicology studies are conducted to reveal the effect of the drug candidate on mammalian reproduction and whether potential reproductive risks may exist for humans. These reproductive studies commonly use pregnant rats and rabbits as the test species. To ensure that the dams and the fetuses are appropriately exposed to the drug candidate and metabolites (11), the dams can be dosed with radiolabeled compound, and the amount of radioactivity that crosses the placenta and into the fetuses at various times after dosing can be determined. If little or no radioactivity is detected in the fetuses, then the ability of animal reproductive studies to predict risks in humans has to be questioned, inasmuch as humans may have a different delivery profile than the animal models. Similarly, the exposure of the drug candidate to nursing pups can be ascertained after the dam is dosed with radiolabeled compound, and the amount of radioactivity excreted in the milk is determined. If little or no radioactivity is detected in the dam's milk, then potential risk to nursing humans cannot be ascertained. When reproductive toxicology studies show no apparent effect, fetal-placenta transfer and lacteal secretion studies can be used to certify these findings and demonstrate that the animals were appropriately exposed to the drug candidate.

C. Toxicology

1. Chronic Studies

Regulatory agencies require chronic toxicity studies in two species, a rodent and a nonrodent, for drug candidates that are to be administered to humans for more than 3 months (8). The two basic reasons for conducting chronic studies are to produce a toxic effect and to define a safety factor. The study should provide a dose-response relationship to effects resulting from prolonged exposure to the drug candidate and should reveal adverse effects that require a long exposure to be expressed or that are cumulative.

Chronic studies often can be conducted in species whose metabolism is most similar to humans, because early human evaluations most likely have been completed before these chronic studies are initiated. The rat is the most common rodent species used in chronic studies, whereas the beagle dog and nonhuman primates are the usual nonrodent species. The dog, a carnivore, often metabolizes compounds differently from humans and should be used with caution. However, nonhuman primates have not been shown to have metabolic systems any closer to humans than most other laboratory animals, but they are the preferred species for macromolecules, because they are similar to humans in anatomy and physiology.

The duration for chronic toxicology studies depends on the projected duration of administration to humans (Table 1). The present consensus according to the FDA (5) is that 6-month rodent and nonrodent studies are sufficient for drug candidates intended for long-term human use, provided the candidate is studied in rats, or other appropriate species, to evaluate the potential for tumor production.

Dose selection for chronic studies is very important, because regulatory agencies want one dose to be a no-toxic-effect dose level and another to show frank toxicity. Several approaches are available to select doses, as described in the section on carcinogenicity studies. However, the most common approach historically has been to use the MTD as the high-dose level for chronic toxicology studies. The MTD has been defined as the dose that, at a minimum, suppresses body weight gain by approximately 10%. The mid- and low-dose levels are based on the MTD and have usually been one quarter of the MTD for the mid-dose and one eighth of the MTD for the low dose. Using this approach, the low dose may be substantially above or even below the expected human therapeutic dose.

2. *Reproductive Toxicology*

Reproductive toxicology studies are designed and conducted to reveal any effect of a drug candidate or a metabolite on mammalian reproduction and to ascertain the potential risks to humans. These studies evaluate male and female fertility, embryo and fetal death, parturition and the newborn, the lactation process, care of the young, and the potential teratogenicity of the drug candidate. Historically, these reproductive parameters have been evaluated in three types of studies, generally referred to as segment I, segment II, and segment III. Segment I evaluates fertility and general reproductive performance in rats. Segment II, commonly conducted in rats and rabbits, determines the embryo toxicity or teratogenic effects of the drug candidate. Segment III, designated the perinatal and postnatal study and normally conducted only in rats, assesses the effects of the drug candidate on late fetal development, labor and delivery, lactation, neonatal viability, and growth of the newborn. Other rodents and nonrodent species, such as mice, guinea pigs, mini pigs, ferrets, hamsters, dogs, and nonhuman primates, have been used to evaluate the reproductive toxicity of drug candidates.

According to an ICH Guideline, (14) the combination of studies selected needs to allow exposure of mature adults and all stages of development from conception to sexual maturity to conception in the following generation. This integrated sequence has been subdivided into various stages, which are designated (A) premating to conception, (B) conception to implantation, (C) implantation to closure of the hard palate, (D) closure of the hard palate to the end of pregnancy, (E) birth to weaning, and (F) weaning to sexual maturity. Using these designations, segment I evaluates stages A and B of the reproductive process, segment II studies stages C and D, and segment III detects adverse effects during stages C to F. A common practice is to combine segments I and III into a single study and conduct separate segment II studies in rats and rabbits.

Segment I studies, designed to evaluate fertility and general reproductive performance (stages A and B), uses sexually mature male and female rats. Male fertility is determined by premating dosing of at least 4 weeks and with dosing continuing throughout the mating period. Histopathology of the testes and sperm analysis are used to detect effects on spermatogenesis (15). Female fertility is determined by premating dosing of at least 14 days with dosing continuing during the mating period. A mating ratio of 1 : 1 is recommended, and documentation should allow identification of both parents of a litter. Copulation is evaluated daily by vaginal smears or by observation of the copulatory plug. Day 0 of gestation is when proof of copulation is discovered. Half of the females are sacrificed at a point after midpregnancy, usually day 13 of gestation, and are examined for the number and distribution of embryos in each uterine horn, embryos undergoing resorption, and the presence of empty implantation sites. Males are sacrificed at any time after mating and assurance of successful induction of pregnancy. The other half of the females are allowed to deliver normally, and the litter size, number per litter alive or dead, and any abnormal observations during gross examination are noted.

Segment II, or teratology studies, are designed to ascertain if a drug candidate has potential for embryotoxicity or teratogenic effects (stages C and D) and are conducted in a rodent and nonrodent species. The drug candidate is administered during the period of organogenesis, which is usually considered gestation day 6 to 15 for mice and rats and gestation day 6 to 18 for rabbits. Fetuses are delivered by Cesarean section a day or two before anticipated parturition. For rats, half of the fetuses are examined for visceral alterations, and the other half are evaluated for skeletal abnormalities. For rabbits, microdissection techniques for soft tissue alterations allow all of the fetuses to be examined for both soft tissue and skeletal abnormalities.

Segment III studies are usually conducted only in rats and are designed to evaluate effects on perinatal and postnatal development of pups and on maternal function (stages C to F). The drug candidate is administered to the dams from implantation to the end of lactation (stages C to E). At the time of weaning, normally one male and one female offspring per litter are selected for rearing to adulthood and mating to assess reproductive competence. These offspring can also be evaluated by use of behavioral and other functional tests for the study of physical development, sensory functions and reflexes, and behavior. The dams and other pups are sacrificed at the time of weaning and evaluated histopathologically.

As with most toxicology studies, three dose levels and a vehicle control group are recommended for reproductive studies. Commonly, a dose-range-finding study, which can incorporate toxicokinetic evaluation, is conducted in pregnant animals, which may be more susceptible to toxic effects, to define the dose levels, one of which should produce frank signs of toxicity and another that should be a no-toxic-effect dose. As noted earlier, drug metabolism studies are sometimes conducted to demonstrate that the dams and the fetuses have been appropriately exposed to the drug candidate.

3. *Carcinogenicity*

Carcinogenicity studies encompass most of the test species' life span and are designed to measure tumor induction in animals and to assess the relevant risk in humans (16). These studies are normally conducted concurrently with phase 3 human clinical trials and are required by regulatory agencies when human exposure to a drug candidate is anticipated to be more than 6 months. For drug candidates being developed to treat certain life-threatening diseases, carcinogenicity studies may be concluded after marketing approval but should be started during human clinical testing. Carcinogenicity studies should be initiated earlier in the drug development process when: (a) the drug candidate or a known metabolite is structurally related to a known carcinogen, (b) a special aspect of the drug candidate's biological action (e.g., members of the therapeutic class have shown a positive carcinogenic response) causes concern, (c) the drug candidate produces toxicities in early studies that are indicative of preneoplastic changes, (d) the drug candidate or a metabolite shows evidence of accumulation in organ systems, and (e) mutagenicity tests suggest that the drug candidate may be a potential carcinogen. Some companies combine chronic toxicity and carcinogenicity studies in the rat by appropriately increasing the sizes of each dose group.

Mice and rats, with life spans of approximately 18 and 24 months, respectively, are normally used in carcinogenicity studies because of economy of these species, their susceptibility to tumor induction, and the large database available on their physiology and pathology. If other nonclinical or clinical results suggest that the rodent is an inappropriate model, carcinogenicity studies in other species, such as the dog for the development of birth control drugs, can be conducted. An ICH Guideline (17) suggests that one rodent (usually the rat) carcinogenicity study plus one other study, usually a subchronic or chronic in vivo rodent study, may be sufficient to ascertain the carcinogenicity potential of a drug candidate.

When feasible, the route of exposure in the test species should be the same as the clinical route of administration. An alternative route may be used if it gives similar metabolism and systemic exposure, particularly to relevant organs, such as the lung for inhalation agents, as the clinical route. Supportive drug metabolism and toxicokinetic data are generally required for selection of an alternative route of administration.

Standard carcinogenicity studies are generally inappropriate for biotechnology-derived pharmaceuticals (12). Macromolecules, unless they are endogenous substances used as replacement therapy, may need to be evaluated for carcinogenic potential if indicated by treatment duration, clinical indication, and patient population. A variety of approaches, such as the ability to support or induce proliferation of transformed cells or to simulate growth of normal or malignant cells expressing a receptor for the drug candidate, can be used to assess risk and are usually compound specific. The study designs and protocols to evaluate carcinogenicity potential of macromolecules should be discussed with the appropriate regulatory agencies before the evaluations are initiated.

Dose selection for carcinogenicity studies has been a topic of discussion for many years. According to an ICH Guideline (18), the selected doses (a) should provide a test species exposure to the drug candidate that allows an adequate margin of safety over the human therapeutic exposure, (b) are tolerated without significant chronic physiologic function impairment and are compatible with good survival, (c) are guided by a comprehensive set of animal and human data that focus on the properties of the drug candidate and the suitability of the test species, and (d) permit data interpretation in the context of proposed clinical use. In all cases, appropriate dose-ranging studies, usually of 90-day duration, need to be conducted.

The approaches that may be appropriate and are acceptable for dose selection include toxicity-based endpoints such as the MTD, pharmacokinetic endpoints, saturation of absorption, pharmacodynamic endpoints, maximum feasible dose, and additional scientifically defensible endpoints. For toxicity-based endpoints, general study design characteristics to establish the MTD include that (a) the rodent species/strains with metabolic profiles as similar as possible to that of humans should be used, (b) dose-ranging studies should be conducted for both males and females for all strains and species to be tested in the carcinogenicity bioassay, (c) dose selection is generally determined from 90-day studies with the route and method of administration that will be used in the bioassay, (d) selection of an appropriate dosing schedule and regimen should be based on clinical use and exposure patterns, pharmacokinetics, and practical considerations, (e) both the toxicity profile and any dose-limiting toxicity should be characterized, with consideration given to the occurrence of preneoplastic lesions or tissue-specific proliferative effects and disturbances in endocrine homeostasis, and (f) changes in metabolite profile or alterations in metabolizing enzyme activities (induction or inhibition) over time should be understood to allow for appropriate interpretation of results from the studies.

Systemic exposure of the drug candidate in the test species that represents a large multiple of human exposure, based on the plasma concentration versus time curve (AUC), at the maximum proposed human daily dose may be used for carcinogenicity study dose selection. The AUC is the most comprehensive pharmacokinetic endpoint, because this value includes both the plasma concentration of the drug candidate and the residence time in vivo. For pharmacokinetic endpoints to be used for dose selection, the information needed to establish the recommended 25-fold ratio of rodent to human normalized (using mg/m^2 dose levels) AUC include that (a) rodent pharmacokinetic data are derived with the use of the test species strains, the route of administration, and dose ranges planned for the carcinogenicity study, (b) bioanalytical methods, which have been appropriately validated, are used to determine plasma concentrations of the drug candidate in both rodents and humans, (c) pharmacokinetic data are derived from studies of sufficient duration to take into account potential time-dependent changes in pharmacokinetic parameters, which may be detected from toxicokinetic results obtained during the dose-ranging studies, (d) documentation is available on the similarity of metabolism between the test species and humans, (e) in the assessment of exposure, scientific judgment is used to determine whether the AUC comparison is based on data for the parent, parent and metabolite(s), or metabolite(s), and justification for the decision is provided, (f) interspecies differences in protein binding are taken into consideration when relative exposure is estimated, and (g) human pharmacokinetic data are obtained from studies encompassing the maximum recommended human daily dose.

For saturation of absorption to be used for dose selection, information that the absorption process has been saturated using the intended route of administration is necessary. These data can usually be obtained during well-designed pharmacokinetic studies that evaluate linearity of absorption and dose proportionality using the route and frequency of dosing projected for human clinical studies.

The use of pharmacodynamic end points for high-dose selection is considered to be highly compound specific and is considered for individual study designs on the basis of scientific merit. The high dose should produce a pharmacodynamic response in the test species that precludes further dose escalation but does not produce disturbances of physiology or homeostasis that would compromise the validity of the carcinogenicity study. Examples of such pharmacodynamic endpoints include hypotension and inhibition of blood clotting.

The use of maximum feasible dose for dose selection is usually applicable only to studies using dietary administration of the drug candidate. When routes other than dietary administration are used, the high dose may be limited because of practicality and local tolerance. The use of pharmacokinetic endpoints for dose selection should significantly decrease the need to select the high dose for carcinogenicity studies based on feasibility criteria.

The mid and low doses for a carcinogenicity study are to provide information for assessing the relevance of the study findings to humans. The low dose should be equal to, or a multiple of, the maximum dose proposed for human testing. The rationale for the selection of the low and mid dose needs to be provided on the basis of pharmacokinetic linearity and saturation of metabolic pathways, human exposure and therapeutic dose, pharmacodynamic response in the test species, alteration in the normal physiology of the test species, mechanistic information and the potential for threshold effects, and the unpredictability of toxicity progression observed in other toxicology studies.

VII. CONCLUSION

This chapter has provided information on the nonclinical aspects of the drug development process. As described, the biological stages of nonclinical development normally proceed linearly (a) from drug discovery, when the pharmacology of a lead candidate is evaluated in animal models to show that the compound has the potential to mediate a human disease, (b) to developability assessment, which provides preliminary data on the pharmacokinetics, drug delivery, and toxicology of the lead candidate to ascertain if the compound has the necessary attributes to enter the drug development process, (c) to preclinical evaluations, when the necessary drug safety studies are conducted to support the submission of an IND, and (d) finally to nonclinical studies, which extend information on the metabolism and toxicity of the drug candidate and show that the earlier animal studies are predictive of human pharmacologic and toxicologic responses. Careful design, conduct, and interpretation of the results from these nonclinical research experiments normally determine which discovery leads have the necessary attributes to become marketed human therapeutic products. These experiments can be used to "weed out" those candidates that have unacceptable pharmacology or toxicology profiles before, or shortly after, the initiation of human clinical testing, but definitely before the start of phase 3 clinical studies, which are the most expensive aspect of drug development in terms of both time and dollars (Figure 1). If most, or at least many, of the estimated 3,999 out of 4,000 "loser" candidates can be detected earlier in the drug development process and dropped from further evaluation, the precious time and resources needed to support clinical and nonclinical drug development studies can be devoted to drug candidates that have a greater potential of successfully completing the studies necessary for the submission of an NDA.

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3

The Investigational New Drug Application and the Investigator's Brochure

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I. OVERVIEW

The Federal Food, Drug and Cosmetic Act prohibits the shipment of a new drug into interstate commerce unless there exists for that drug an approved NDA or an effective IND application. Unlike certain European countries, such as Germany and the United Kingdom, the existence of an IND is required regardless of the proposed phase of clinical trial. Thus, even phase 1 trials to be conducted in the United States on volunteer subjects require the prior submission of an IND before that trial may be undertaken.

The requirements for the format and content of the IND application, as well as the requirements governing the use of the IND, are provided in Title 21 of the Code of Federal Regulations (21 CFR), Section 312. Unlike an NDA, the FDA does not formally "approve" an IND submission. If the FDA reviewers believe that the proposed clinical trial(s) submitted in the IND are acceptable from a safety and risk *versus* benefit viewpoint, the IND is in "effect," and the compound that is the subject of that IND may be shipped in interstate commerce for the purpose of conducting specific clinical trials. Drugs shipped under an IND have specific labeling requirements, and false or misleading statements, as well as any claims regarding safety and efficacy, are prohibited.

This chapter will provide information that is necessary to achieve a successful IND submission to the FDA. It will focus on the differences between the requirements for an IND submitted to permit a phase 1 trial as contrasted to IND submissions intended to support phase 2 or 3 clinical research. Finally, it will also detail the requirements for the investigator's brochure, the document that summarizes the known safety and efficacy information about the drug that will be submitted to potential investigators and to IRBs and as part of the IND document itself.

II. THE INVESTIGATIONAL NEW DRUG APPLICATION

A. Introduction

An IND may be submitted to the FDA by a commercial organization (the "sponsor") or by a clinical investigator (the "investigator"). The sponsor or investigator may not commercially distribute or test market an investigational new drug, nor may an investigation be unduly prolonged after the finding that the results of the investigation appear to establish sufficient data to support a marketing application. Under certain defined circumstances described in 21 CFR Part 312.7, a sponsor may charge the patient for an investigational drug, but this is atypical and can be done only after written approval from the FDA.

B. General Information Regarding INDs

1. Exemptions

The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of an IND providing all of the following apply: (a) the investigation is neither intended to be reported to the FDA as a well-controlled study in support of a new indication for use nor to be used to support any other significant change in the labeling for the drug, (b) if the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product, (c) the investigation does not involve a route of administration nor dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product, and (d) the investigation is conducted in compliance with the requirements for institutional review approval and the requirements for informed consent as discussed elsewhere in this book.

2. Labeling Requirements for an Investigational New Drug

Labeling for a drug covered by an IND will be discussed under the Chemistry, Manufacturing, and Control requirements for part 7 of the IND; however, independent of the use or indication for the drug and independent of the dosage form, all immediate packages of drug product supplied to a patient involved in an investigational trial require the following statement: "Caution: New Drug—Limited by Federal (or United States) law to investigational use." Additionally, the label or labeling (including the investigator's brochure) shall not bear any statement that is false or misleading to possibly represent the investigational new drug as being safe or effective for the purposes for which it is being investigated.

3. Waivers

In rare instances, the FDA may grant a waiver to the requirements for an IND on the basis of a justified request from the sponsor. Acceptable justification may include an explanation of why the sponsor's compliance is unnecessary or cannot be achieved or a description of an alternative means of satisfying the requirement. The FDA may grant such a request for a waiver if it determines that the sponsor's noncompliance would not pose a significant or unreasonable risk to the human test subjects.

4. Preconsultation Program

At this time, only one division within the Center for Drug Evaluation and Research, the Division of Antiviral Drug Products (DAVDP), has established a pre-IND consultation program. This program, established in 1988, is a proactive strategy designed to facilitate informal early communications between DAVDP and the potential sponsor of new therapeutics for the treatment of AIDS and life-threatening opportunistic infections, other viral infections, and soft tissue transplantations. Pre-IND advice may be requested for issues related to drug development plans, data needed to support the rationale for testing a drug in humans, the design of nonclinical pharmacology, toxicology, and drug activity studies, data requirements for IND applications, and regulatory requirements for demonstrating safety and efficacy. Details on requesting information about this program or on how to participate in this preconsultation program may be found on the internet.

For INDs to be submitted to other divisions, on the sponsor's request, the FDA will provide advice on specific matters relating to an IND. Examples may include advice on the adequacy of technical data to support an investigational plan, on the design of a clinical trial, and on whether proposed investigations are likely to produce the data and information needed to meet requirements for a marketing application. It should be noted, however, that unless the communication is accompanied by a clinical hold, FDA communications with a sponsor regarding pre-IND information is solely advisory and does not require any modification in the planned or ongoing clinical investigations or response to the agency.

5. *Binders for IND Submissions*

The FDA has specific requirements for the type and color of binders in which an IND may be submitted. All INDs and IND amendments are submitted to FDA in triplicate. The original IND submission (copy 1) is to be submitted in a red binder, and copies 2 and 3 are submitted in green and orange binders, respectively. Effective April 1, 1998, sponsors may call the U.S. Government Printing Office (GPO) to order FDA IND, NDA, ANDA, and Drug Master File binders. The red binder is Form No. 2675, and the green and orange binders are Form No. 2675a and 2675b, respectively. The GPO may be contacted by telephone at (202) 512-1800 or by mail at U.S. Government Printing Office, Washington, DC 20404-0001. In either instance, reference should be made to Program #B511-S. Details on the required specifications for the FDA's binders may also be obtained from the internet at http://www.fda.gov/cder/ddms/binders.htm.

6. *Address for IND Submissions*

An initial IND submission is to be sent in triplicate to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, Park Building, Room 214, 12420 Parklawn Drive, Rockville, Maryland 20852. Upon receipt of the IND, the FDA will inform the sponsor which one of the divisions in the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research is responsible for the IND.

Once the IND is in effect, amendments, reports, and other correspondence relating to matters covered by the IND should be directed to the appropriate division. The outside wrapper or cover letter of each submission should state what is contained in the submission, for example "IND Application," "Protocol Amendment," etc.

Specific address information relating to submission of applications for products subject to the licensing provisions of the Public Health Service Act of July 1, 1944, urokinase products, plasma volume expanders, coupled antibodies, and biological products that are also radioactive drugs are described in 21 CFR Part 312.140.

7. *Availability for Public Disclosure of IND Data*

The manner in which FDA handles requests for disclosure of information to the public under the Freedom of Information Act is described in 21 CFR Part 312.130. The existence of an IND will not be disclosed by the FDA unless it has previously been publicly disclosed or acknowledged by the sponsor. However, upon request, the FDA will disclose to an individual to whom an investigational new drug has been given a copy of any IND safety report relating to the use in the individual.

C. Phases of Clinical Investigations

As noted previously, the FDA has recently clarified the requirements for an IND intended for phase 1 clinical trials compared with trials that are designed for phase 2 or 3 clinical programs. Table 1 provides information regarding the differences between the phases of investigation with respect to the size and scope of the particular phase. A more detailed description of the phases of investigation may be found in 21 CFR Part 312.21.

Phase 1 includes the initial introduction of an investigational new drug into humans. These studies are typically closely monitored and may be conducted in patients or in normal volunteer subjects. They are designed to determine the metabolism and pharmacologic actions of the drug in humans and the side effects associated with increasing doses and sometimes to gain early evidence on effectiveness. The results of the phase 1 program concerning the drug's pharmacokinetic and pharmacologic effects will be obtained to permit the design of well-controlled and scientifically valid phase 2 trials.

Phase 2 includes the controlled clinical studies conducted to evaluate the appropriate dose-range and effectiveness of the drug for a particular indication in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects.

Expanded controlled and uncontrolled trials comprise the phase 3 program. They are performed after preliminary evidence suggesting a knowledge

Table 1 Phases of Clinical Investigation

Phase	Number of Patients	Length	Purpose	Percent of Drugs Successfully Tested*
1	20–200	Several months	Mainly safety	70%
2	Up to several hundred	Several months to 2 years	Some short-term safety, dosage and effectiveness	33%
3	Several hundred to several thousand	1 to 4 years	Safety, dosage, effectiveness	25%–30%

*For example, of 100 drugs for which IND applications are submitted to the FDA, about 70 will successfully complete phase 1 trials and go on to phase 2; about 33 of the original 100 will complete phase 2 and go to phase 3; and 25 to 30 of the original 100 will clear phase 3 (and, on average, about 20 of the original 100 will ultimately be approved for marketing).

of the proper dosage and effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling.

1. Phase 1

a. INDs for Phase 1 Studies

The FDA has recently assessed means to increase the efficiency of the drug development process without sacrificing the long-standing safety and efficacy standards expected by the public for their drug products to meet.

In November 1995, CDER and CBER issued a Guidance for Industry entitled, *Content and Format of Investigational New Drug Applications for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products*. This guidance clarified the requirements for data and data presentation related to the initial entry into human studies in the United States of an investigational drug, including well-characterized, therapeutic, biotechnology-derived products. The FDA emphasized that the IND regulations allowed a great deal of flexibility in the amount and depth of various data to be submitted in an IND, depending in large part on the phase of investigation and the specific human testing being proposed. In some cases, the extent of that flexibility had not been appreciated by industry. Thus, the guidance was developed to clarify many of the phase 1 IND requirements to help expedite entry of new drugs into clinical testing by increasing transparency and by reducing ambiguity, inconsistencies, and the amount of information submitted, while providing the FDA with the data it needs to assess the safety of the proposed phase 1 study. According to the guidance, if the suggestions specified in the document are followed, typical IND submissions for phase 1 studies usually should not be larger than two to three 3-inch binders.

The most significant clarifications in the guidance document are (a) the explicit willingness of the FDA to accept an integrated summary report of toxicology findings based on the unaudited draft toxicologic reports of completed animal studies as initial support for human studies, and (b) specific manufacturing data appropriate for a phase 1 investigation. Because of the manufacturing and toxicologic differences between well-characterized, therapeutic, biotechnology-derived products and other biologic products, the FDA emphasized that the guidance applies only to drugs and well-characterized, therapeutic, biotechnology-derived products. For products not covered by this phase 1 guidance, it is recommended that the center responsible for the product be contacted for specific information.

b. Requirements for Protocols

The regulation requires submission of a copy of the protocol for the conduct of each proposed clinical trial. However, the regulations were changed in 1987 specifically to allow phase 1 study protocols to be less detailed and more flexible than protocols for phase 2 or 3 studies. This change recognized that these protocols are part of an early learning process and should be adaptable as information is obtained, and that the principal concern at this stage of development is that the study be conducted safely. The regulations state that phase 1 protocols should be directed primarily at providing an outline of the investigation: an estimate of the number of subjects to be included; a description of safety exclusions; and a description of the dosing plan, including duration, dose, or method to be used in determining dose. In addition, such protocols should specify in detail only those elements of the study that are critical to subject safety, such as (a) necessary monitoring of vital signs and blood chemistries, and (b) toxicity-based stopping or dose adjustment rules. The regulations also state that modifications of the experimental design of phase 1 studies that do not affect critical safety assessments are required to be reported to FDA only in the IND Annual Report.

c. *Requirements for CMC Information*

The IND regulations emphasize the graded nature of manufacturing and control information that is required to be submitted. Although in each phase of the investigation, sufficient information should be submitted to assure the proper identification, quality, purity, and strength of the investigational drug, the amount of information needed to make that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available. For example, although stability data are required in all phases of the IND to demonstrate that the new drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation, if very short-term tests are proposed, the supporting stability data also can be very limited.

It is recognized that modifications to the method of preparation of the new drug substance and dosage form, and even changes in the dosage form itself, are likely as the investigation progresses. Emphasis in an initial phase 1 CMC submission should generally be placed on providing information that will allow evaluation of the safety of subjects in the proposed study. The identification of a safety concern or insufficient data to make an evaluation of safety is the only basis for a clinical hold based on the CMC section.

Reasons for concern may include (a) a product made with unknown or impure components, (b) a product possessing chemical structures of known or highly likely toxicity, (c) a product that cannot remain chemically stable throughout the testing program proposed, (d) a product with an impurity profile indicative of a potential health hazard or an impurity profile insufficiently defined to assess a potential health hazard, or (e) a poorly characterized master or working cell bank.

In addition, for preclinical studies to be useful in assuring the safety of human studies, sponsors should be able to relate the drug product being proposed for use in a clinical study to the drug product used in the animal toxicology studies that support the safety of the proposed human study.

The following information will usually suffice for a meaningful review of the manufacturing procedures for drug products used in phase 1 clinical studies. As will be discussed later in this chapter, additional information should ordinarily be submitted for review of the larger-scale manufacturing procedures used to produce drug products for phase 2 or 3 clinical trials or as part of the manufacturing section of an NDA.

The CMC Section Introduction. At the beginning of this section, the sponsor should state whether it believes (a) the chemistry of either the drug substance or the drug product, or (b) the manufacturing of either the drug substance or the drug product, presents any signals of potential human risk. If so, these signals of potential risks should be discussed. The steps proposed to monitor for such risk(s) should be described or the reason(s) why the signal(s) should be dismissed should be discussed. In addition, sponsors should describe any chemistry and manufacturing differences between the drug product proposed for clinical use and the drug product used in the animal toxicology trials that formed the basis for the sponsor's conclusion that it was safe to proceed with the proposed clinical study. How these differences might affect the safety profile of the drug product should be discussed. If there are no differences in the products, that should be stated.

The Drug Substance. It should be noted that references to the current edition of the USP-NF may be used to satisfy some of the requirements of this section, when applicable. Information on the drug substance should be submitted in a summary report containing the following items:

1. Description: A brief description of the drug substance and some evidence to support its proposed chemical structure should be submitted. It is understood that the amount of structure information will be limited in the early stage of drug development.

2. The name and address of its manufacturer: The full street address of the manufacturer of the clinical trial drug substance should be submitted.

3. Method of preparation: A brief description of the manufacturing process, including a list of the reagents, solvents, and catalysts used, should be submitted. A detailed flow diagram is suggested as the usual, most effective presentation of this information. However, more information may be needed to assess the safety of biotechnology-derived drugs or drugs extracted from human or animal sources.

4. Tests and analytical methods: A brief description of the test methods used should be submitted. Proposed acceptable limits supported by simple analytical data (e.g., IR spectrum to prove the identity and HPLC chromatograms

to support the purity level and impurities profile) of the clinical trials material should be provided. Submission of a copy of the certificate of analysis is also suggested. The specific methods will depend on the source and type of drug substance (e.g., animal source, plant extract, radiopharmaceutical, other biotechnology-derived products). Validation data and established specifications ordinarily need not be submitted at the initial stage of drug development. However, for some well-characterized, therapeutic, biotechnology-derived products, preliminary specifications and additional validation data may be needed in certain circumstances to ensure safety in phase 1.

5. Stability data: A brief description of the stability study and the test methods used to monitor the stability of the drug substance should be submitted. Preliminary tabular data based on representative material may be submitted. Neither detailed stability data nor the stability protocol should be submitted.

The Drug Product. It should be noted that references to the current edition of the USP-NF may be used to satisfy some of the requirements of this section, when applicable. Information on the drug product should be submitted in a summary report containing the following items:

1. A list of all components: A list of usually no more than one or two pages of written information should be submitted. The quality (e.g., NF, ACS) of the inactive ingredients should be cited. For novel excipients, additional manufacturing information may be necessary.
2. Quantitative composition: A brief summary of the composition of the investigational new drug product should be submitted. In most cases, information on component ranges is not necessary.
3. The name and address of the manufacturer: The full street address(es) of the manufacturer(s) and packager of the clinical trial drug product should be submitted.
4. Method of manufacturing and packaging: A diagrammatic presentation and a brief written description of the manufacturing process should be submitted, including the sterilization process for sterile products. Flow diagrams are suggested as the usual, most effective presentations of this information.
5. Acceptable limits and analytical methods: A brief description of the proposed acceptable limits and the test methods used should be submitted. Tests that should be submitted will vary according to the dosage form. For example, for sterile products, sterility and nonpyrogenicity tests should be submitted. Submission of a copy of the certificate of analysis of the clinical batch is also suggested. Validation data and established specifications need not be submitted at the initial stage of drug development. For well-characterized, therapeutic, biotechnology-derived products, adequate assessment of bioactivity and preliminary specifications should be available.
6. Stability testing: A brief description of the stability study and the test methods used to monitor the stability of the drug product packaged in the pro-

posed container/closure system and storage conditions should be submitted. Preliminary tabular data based on representative material may be submitted. Neither detailed stability data nor the stability protocol need to be submitted.

7. Placebo: If any placebo dosage form is to be used in the phase 1 trial, diagrammatic, tabular, and brief written information should be submitted.

8. Labeling: A mock-up or printed representation of the proposed labeling that will be provided to investigators in the proposed clinical trial should be submitted. Investigational labels must carry a "caution" statement as stated earlier. The required statement reads: "Caution: New Drug—Limited by Federal (or United States) law to investigational use."

9. Environmental assessment: The FDA believes that the great majority of products will qualify for a categorical exclusion. Sponsors who believe that their investigational product meets the exclusion categories under 21 CFR 25.24 should submit a statement certifying that their product meets the exclusion requirements and request a categorical exclusion on that basis. (For INDs submitted to CDER, it is recommended to review the FDA guidance entitled: *Guidance for Industry for the Submission of Environmental Assessments for Human Drug Applications and Supplements*, November, 1995.)

Pharmacology and Toxicology Information. Pharmacology and drug distribution: This section of the phase 1 IND should contain, if known, (a) a description of the pharmacologic effects and mechanism of action of the drug in animals, and (b) information on the absorption, distribution, metabolism, and excretion of the drug. The regulations do not describe the presentation of these data. A summary report, without individual animal records or individual study results, usually suffices. In most circumstances, five pages or less should be adequate for this summary. To the extent that such studies may be important to address safety issues or to assist in evaluation of toxicology data, they may be necessary; however, lack of this potential effectiveness information generally should not be a reason for a phase 1 IND to be placed on clinical hold.

Toxicology—integrated summary: The IND regulations require an integrated summary of the toxicologic effects of the drug in animals and in vitro. The particular studies needed depend on the nature of the drug and the phase of human investigation. The regulations are not specific as to the nature of the report of toxicology data needed in an IND submission and the nature of the study reports upon which the report submitted to the IND is based. Also, the IND regulations are silent on whether the submitted material should be based on (a) "final, fully quality-assured" individual study reports, or (b) earlier, unaudited draft toxicologic reports of the completed studies. In the past, most sponsors have concluded that a submission based on final, fully quality-assured individual study reports is required, and a substantial delay in submission of an IND for several months is often encountered to complete such final, fully quality-assured individual reports from the time the unaudited draft toxicologic reports of the completed studies are prepared.

Moreover, although the regulation does not specifically require individual toxicology study reports to be submitted, referring only to an integrated summary of the toxicologic findings, the requirement for a full tabulation of data from each study suitable for detailed review has led most sponsors to provide detailed reports of each study.

Although the GLP and quality assurance processes and principles are critical for the maintenance of a toxicology study system that is valid and credible, it is unusual for findings in the unaudited draft toxicologic report of the completed studies to change during the production of the "final," quality-assured individual study reports in ways important to determining whether use in humans is safe.

Therefore, for a phase 1 IND, if final, fully quality-assured individual study reports are not available at the time of IND submission, an integrated summary report of toxicologic findings based on the unaudited draft toxicologic reports of the completed animal studies may be submitted. This integrated summary report should represent the sponsor's evaluation of the animal studies that formed the basis for the sponsor's decision that the proposed human studies are safe. It is expected that the unaudited draft reports that formed the basis of this decision might undergo minor modifications during final review and quality assurance auditing. Full toxicology department individual study reports and individual study reports should be available to the FDA, upon request, as final, fully quality-assured documents within 120 days of the start of the human study for which the animal study formed part of the safety conclusion basis. These final reports should contain in the introduction any changes from those reported in the integrated summary. If there are no changes, that should be clearly stated at the beginning of the final, fully quality-assured report.

If the integrated summary is based upon unaudited draft reports, sponsors should submit an update to their integrated summary by 120 days after the start of the human studies identifying any differences found in the preparation of the final, fully quality-assured study reports and the information submitted in the initial integrated summary. If no differences were found, that should be stated in the integrated summary update. In addition, any new finding discovered during the preparation of the final, fully quality-assured individual study reports that could affect subject safety must be reported to the FDA as an IND safety report.

Usually, 10 to 15 pages of text with additional tables as needed should suffice for the integrated summary. It should represent a perspective on the completed animal studies at the time the sponsor decided that human trials were appropriate. Use of visual data displays (e.g., box plots, histograms, or distributions of laboratory results over time) will facilitate description of the findings of these trials. The summary document should be accurate contemporaneously with the IND submission (i.e., it should be updated so that if new information or findings from the completed animal studies have become known since the sponsor's decision that the proposed human study is safe, such new information should also be included in the submitted summary).

The integrated summary of the toxicologic findings of the completed animal studies to support the safety of the proposed phase 1 human investigation should ordinarily contain the following information:

1. A brief description of the design of the trials, dates of performance, and any deviations from the design in the conduct of the trials. Reference to the study protocol and protocol amendments may be adequate for some of this information.
2. A systematic presentation of the findings from the animal toxicology and toxicokinetic studies. Those findings that an experienced expert would reasonably consider as possible signals of human risk should be highlighted. The format of this part of the summary may be approached from a "systems review" perspective (e.g., CNS, cardiovascular, pulmonary, gastrointestinal, renal, hepatic, genitourinary, hematopoietic, immunologic, and dermal). If a product's effects on a particular body system have not been assessed, that should be noted. If any well-documented toxicologic "signal" is not considered evidence of human risk, the reason should be given. In addition, the sponsor should note whether these findings are discussed in the Investigator's Brochure.
3. Identification and qualifications of the individual(s) who evaluated the animal safety data and concluded that it is reasonably safe to begin the proposed human study. This person(s) should sign the summary attesting that it accurately reflects the animal toxicology data from the completed studies.
4. A statement of where the animal studies were conducted and where the records of the studies are available for inspection, should an inspection occur.
5. A declaration that each study subject to GLP regulations was performed in full compliance with GLPs or, if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance and the sponsor's view on how such noncompliance might affect the interpretation of the findings.

It should be noted that the information described in the last three points may be supplied as part of the integrated summary or as part of the full data tabulations described in the next section.

Toxicology—full data tabulation: The sponsor should submit, for each animal toxicology study that is intended to support the safety of the proposed clinical investigation, a full tabulation of data suitable for detailed review. This should consist of line listings of the individual data points, including laboratory data points, for each animal in these trials along with summary tabulations of these data points. To allow interpretation of the line listings, accompanying the line listings should be either (a) a brief (usually a few pages) description (i.e., a technical report or abstract including a methods description section) of the study, or (b) a copy of the study protocol and amendments.

In conclusion, this section has been included to assist sponsors who are preparing an IND submission for a phase 1 trial in the United States. Emphasis was provided on the requirements for submission of chemistry and manufacturing data for the drug substance and the drug product, and for information to be submitted regarding the pharmacologic and toxicologic assessments of the new drug candidate.

If a sponsor has conducted phase 1 trials outside of the United States and believes that there are adequate human safety studies already available, it may not be necessary to conduct any phase 1 trials in the United States. In such a case, the sponsor would prepare an IND and include in the initial IND submission a clinical protocol for phase 2 or 3. This IND, because it will involve exposure of more patients to the drug for the purposes of safety testing as well as efficacy evaluations, will require a greater level and depth of manufacturing and nonclinical data. The next section will describe the requirements for such an advanced-stage IND.

2. *Phase 2 or Phase 3*

As noted in the previous section, the FDA's review of phase 1 submissions focuses on assessing the safety of those investigations. The review by the FDA for submissions of phase 2 and 3 trials will also include an assessment of the scientific quality of the clinical investigations and the likelihood that the investigations will yield data capable of meeting statutory standards for marketing approval.

The central focus of the initial IND submission will be on the general investigational plan and the protocols for specific human studies. Subsequent amendments to the IND that contain new or revised protocols should build logically on previous submissions and should be supported by additional information, including the results of animal toxicology studies or other human studies as appropriate. Annual reports to the IND will serve as the focus for reporting the status of studies being conducted under the IND and should update the general investigational plan for the coming year.

An IND goes into effect 30 days after the FDA receives the IND, unless the FDA notifies the sponsor that the investigations described in the IND are subject to a clinical hold. It is possible, but not usual, that there may be earlier notification by the FDA that the clinical investigations in the IND may begin. When the initial IND is filed, the FDA will notify the sponsor in writing of the date it receives the IND.

A sponsor may ship an investigational new drug to investigators named in the IND (a) 30 days after the FDA receives the IND, or (b) on earlier FDA authorization to ship the drug. Of course, an investigator may not administer an investigational new drug to human subjects until the IND goes into effect and there is compliance with the applicable requirements for protection of human subjects, as described by the IRB and IC regulations.

a. Form FDA 1571

The initial IND and each amendment to the IND is to be submitted in triplicate and to include a completed copy of the 2-page form FDA 1571. A copy of this form is shown in Figure 1. This form and many other FDA forms may be downloaded from the internet at the following location: http://forms.psc.dhhs.gov/fdaforms.htm.

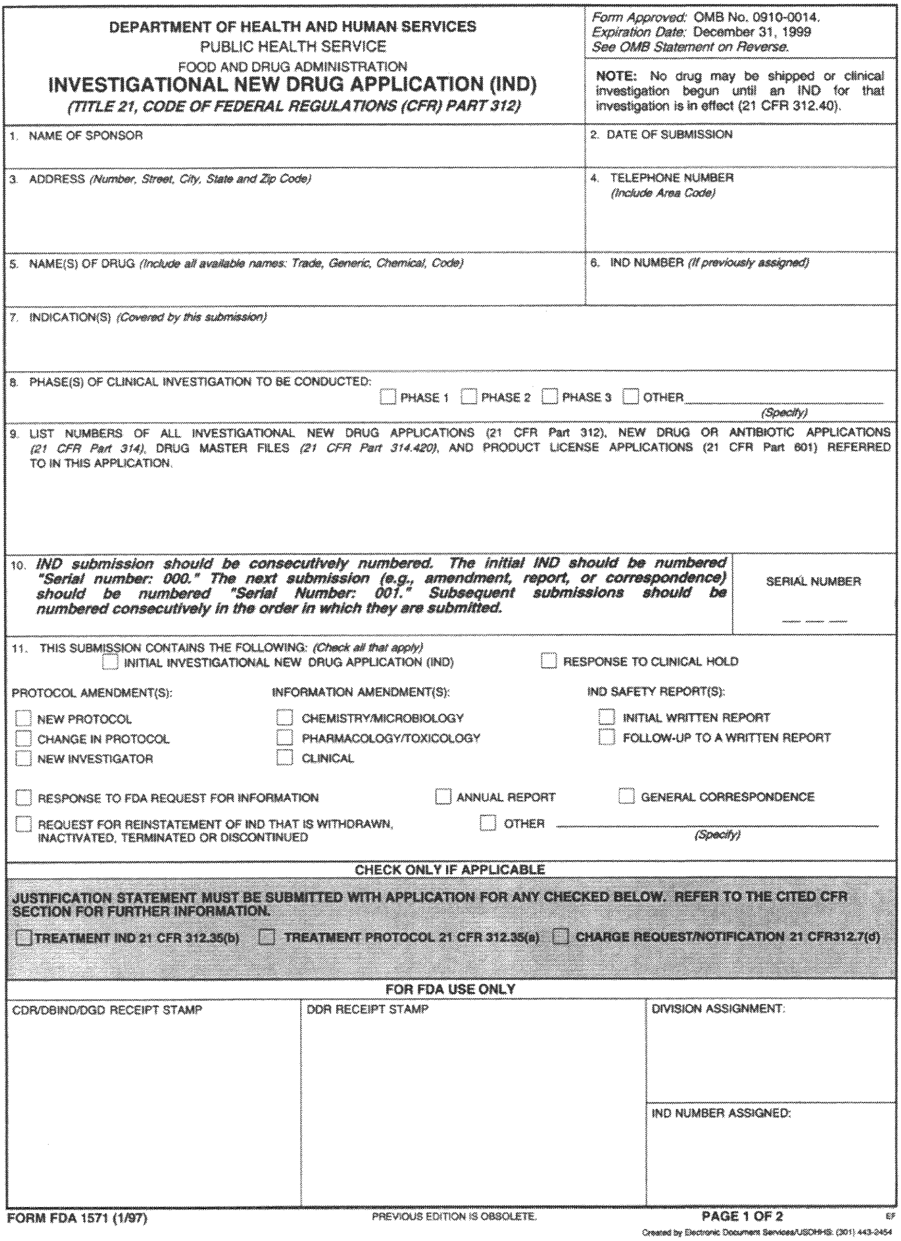
The form contains 20 subitems, each of which must be completed. Items 1, 2, 3, 4, 7, 8, 14, 15, 18, 19, and 20 are self evident and need no further elaboration. Comments on the remaining items are justified.

Item 5 requires the name of the drug. It is cautioned that all names and codes that appear in the IND documentation be added to this space. It is not uncommon that, in the very early stages of preclinical development, a code name is used. As the drug advances in the preclinical stage, a generic name or modified code name may be used. If the early pharmacology or toxicology reports refer to the drug by the earlier code name, this too should be included in item 5.

Item 6, the IND number, will not be inserted at the time of the submission of the initial IND filing. Once the IND is filed, the FDA will assign an IND number, and the sponsor will be notified in writing of this number. From that point forward, every communication between the sponsor and the FDA should include this IND number.

A list of numbers of all referenced applications is needed in item 9. This list will include any referenced drug master files or references to other existing INDs or NDAs on file with the FDA. If the CMC section of the IND refers to the DMF of a container manufacturer for a particular container-closure system, the DMF number and, if possible, the specific pages within that DMF containing information on the container-closure system being used, should be referenced. Similarly, if a previously filed IND or NDA contains pharmacologic or toxicologic data that support the safety of the present IND submission, reference by IND or NDA number, date, volume, and page numbers should be provided in this item.

Each IND submission is serially numbered. It should be noted that the



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: December 31, 1999
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
2. DATE OF SUBMISSION
3. ADDRESS *(Number, Street, City, State and Zip Code)*
4. TELEPHONE NUMBER *(Include Area Code)*
5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
6. IND NUMBER *(If previously assigned)*
7. INDICATION(S) *(Covered by this submission)*
8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER ____________ *(Specify)*
9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.
10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
__ __ __

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) ☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):	INFORMATION AMENDMENT(S):	IND SAFETY REPORT(S):
☐ NEW PROTOCOL	☐ CHEMISTRY/MICROBIOLOGY	☐ INITIAL WRITTEN REPORT
☐ CHANGE IN PROTOCOL	☐ PHARMACOLOGY/TOXICOLOGY	☐ FOLLOW-UP TO A WRITTEN REPORT
☐ NEW INVESTIGATOR	☐ CLINICAL	

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER ____________ *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ **TREATMENT IND 21 CFR 312.35(b)** ☐ **TREATMENT PROTOCOL 21 CFR 312.35(a)** ☐ **CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)**

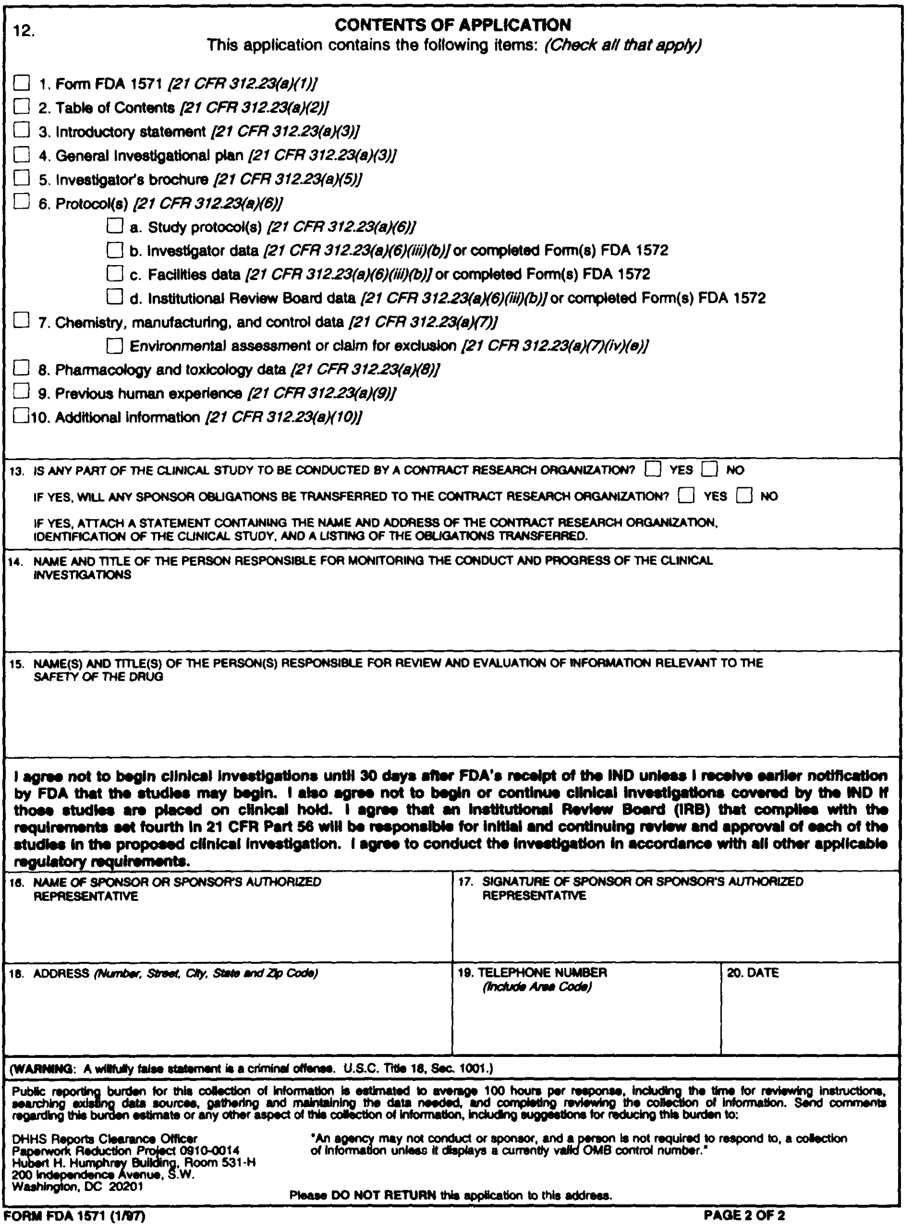
FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	DIVISION ASSIGNMENT:
		IND NUMBER ASSIGNED:

FORM FDA 1571 (1/97) PREVIOUS EDITION IS OBSOLETE. **PAGE 1 OF 2** EF

Created by Electronic Document Services/USDHHS: (301) 443-2454

Figure 1. FDA Form 1571.



12.

CONTENTS OF APPLICATION

This application contains the following items: *(Check all that apply)*

- ☐ 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- ☐ 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- ☐ 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- ☐ 4. General Investigational plan *[21 CFR 312.23(a)(3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- ☐ 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- ☐10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE

(**WARNING**: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS Reports Clearance Officer
Paperwork Reduction Project 0910-0014
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please DO NOT RETURN this application to this address.

FORM FDA 1571 (1/97) PAGE 2 OF 2

Figure 1. Continued.

initial filing of the IND is considered the "000" filing. Once the IND is filed, each amendment to the IND is given a progressively increasing serial submission number from 001 upward. When writing to the FDA about previous filings, the serial submission number may be used to reference the communication.

The appropriate box(es) briefly describing the submission should be checked in item 11. It is possible that one IND amendment may contain protocol amendments and information amendments. In such a case, the applicable boxes are marked. If the filing is for the initial IND, a response to a clinical hold, an initial or follow-up IND safety report, a response to an FDA request for information, an annual report, or general correspondence, the appropriate box should be checked. Finally, there is a box if the sponsor is requesting reinstatement of an IND that has been withdrawn, inactivated, terminated, or discontinued.

The second page of the form FDA 1571 contains items 12–20. Item 12 is a checklist table of contents. Any of the 10 items constituting this table of contents and contained in the specific IND submission for which the form is being prepared should be checked. An initial IND will most likely have all or a majority of the boxes checked. A protocol amendment will have items 1 and all or some of the items 6a–6d checked.

The transfer of obligations of GCP from a sponsor to a CRO is described in detail in 21CFR Part 312.52. A sponsor may transfer responsibility for any or all parts of the GCP obligations to a CRO. Any such transfer is to be described in writing. Conversely, any CRO that assumes any obligation of a sponsor for the requirements of GCP shall comply with the regulations and be subject to the same regulatory action as a sponsor for failure to comply with their assumed obligations. Thus, the purpose of item 13 of the form FDA 1571 is to inform the FDA of whether any part of the clinical study is to be performed by a CRO, and to identify whether the sponsor has transferred the obligations of compliance with GCP to that CRO. Finally, if the response is affirmative, the name and address of the CRO must be provided as part of the IND submission.

Items 16, 18, and 19 are to be completed only if the sponsor of the IND does not have a physical presence in the United States. It is not uncommon for a foreign-based company to sponsor an IND. However, when this occurs, the FDA must have the name, address, and telephone number of a contact person within the United States, as the FDA usually will not contact an overseas company directly. The contact person named by the sponsor may be either a representative within a United States affiliate office or a consultant working on behalf of the foreign sponsor.

b. IND Content and Format

As shown in Figure 1, item 12 of the form FDA 1571 outlines the 10 parts of the IND. This section will detail the requirements for each of those parts and provide illustrations and examples of the items to be presented in the IND. It must be emphasized again that the information to be provided in the following sections represents more complete IND data to support a clinical program in phase 2 or 3. The lesser requirements for phase 1 trials have been discussed previously.

Table of Contents. Once the IND has been formatted and assembled, a detailed table of contents should be prepared. Depending on the size of the initial IND filing, this table of contents may be contained only in volume 1 or preferably included as the first pages of each of the IND volumes. The table of contents should be sufficiently detailed that an FDA reviewer can easily access any specific topic or report contained in the IND. It is also preferable to sequentially number the IND for each volume, rather than to sequentially number the entire IND. Thus, in reference to a specific report or in cross-referencing, it is necessary to provide the volume number and the page number.

The table of contents may have the following headings:

IND Part	Title of Information Provided	Volume	Page

Part 3: Introductory Statement and General Investigational Plan. On the form FDA 1571, the introductory statement appears as part 3 and the general investigational plan appears as part 4 in item 12 of the contents of application (see Figure 1). This is inconsistent with the requirements as detailed in 21 CFR Part 312.23, inasmuch as the introductory statement and general investigation plan are listed only as part 3. Part 4 in the CFR is listed as "Reserved." Thus, the option exists to combine these parts or to present them as separate entities. It is not important which way it is handled. The important thing is to have a clear and concise section, because, as the introduction to the IND, this section is likely to be read not only by the IND reviewers but also by the division director and others within the division.

The introductory statement and general investigational plan will contain the following:

1. A brief introductory statement giving the name of the drug and all active ingredients, the drug's pharmacologic class, the structural formula of the drug (if known), the formulation of the dosage form(s) to be used, the route of administration, and the broad objectives and planned duration of the proposed clinical investigation(s).
2. A brief summary of previous human experience with the drug, with reference to other INDs if pertinent, and to investigational or marketing experience in other countries that may be relevant to the safety of the proposed clinical investigation(s).
3. If the drug has been withdrawn from investigation or marketing in any country for any reason related to safety or effectiveness, identification of

the country(ies) where the drug was withdrawn and the reasons for the withdrawal.

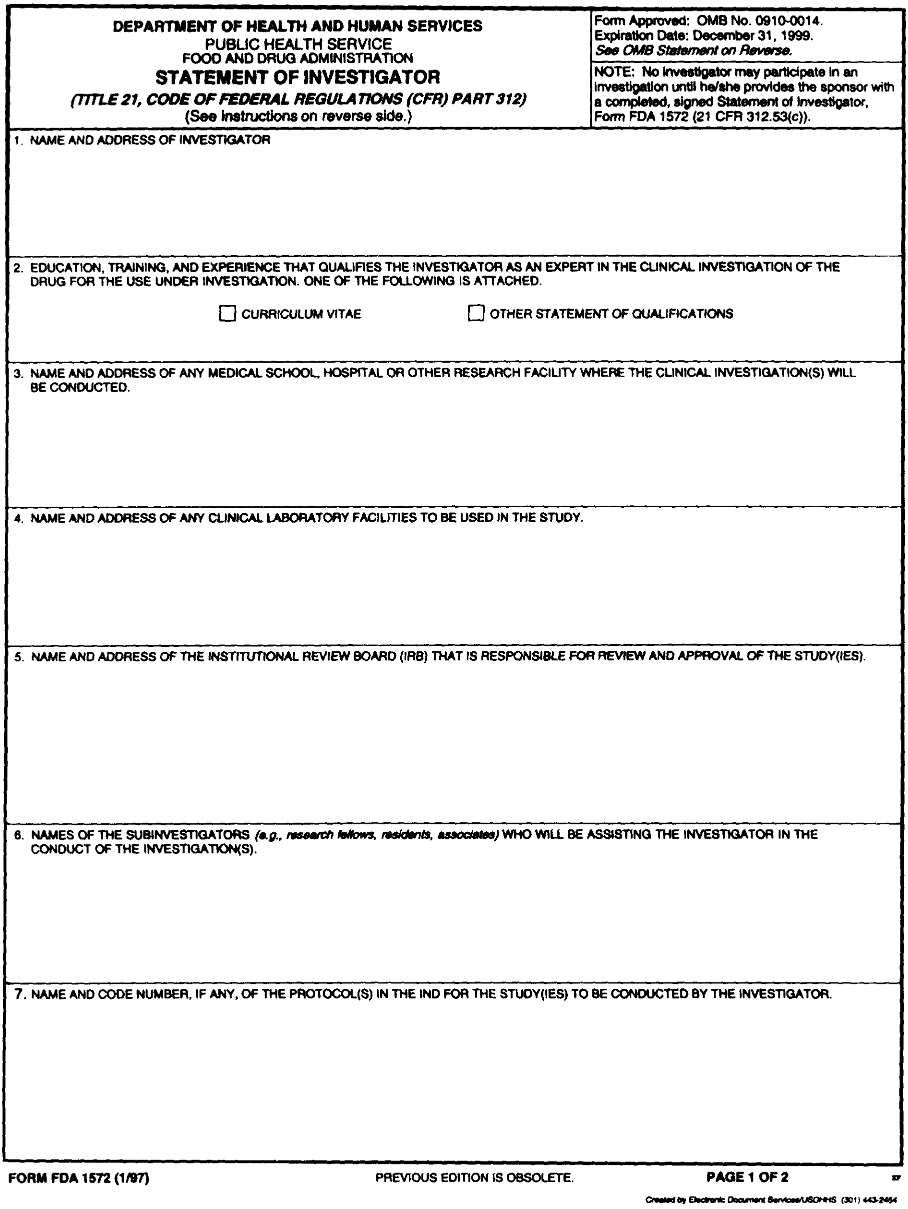
4. A brief description of the overall plan for investigating the drug product for the following year. The plan should include the following: (a) the rationale for the drug or the research study, (b) the indication(s) to be studied, (c) the general approach to be followed in evaluating the drug, (d) the kinds of clinical trials to be conducted in the first year after the submission (if plans are not developed for the entire year, the sponsor should so indicate), (e) the estimated number of patients to be given the drug in those studies, and (f) any risks of particular severity or seriousness anticipated on the basis of the toxicologic data in animals or prior studies in humans with the drug or related drugs.

Part 5: The Investigator's Brochure. This will be covered as a separate topic in this chapter.

Part 6: Protocols and Other Clinical Trial Information. It is necessary to provide at least one protocol in the initial IND submission. If more than one study is planned, a protocol for each planned study should be submitted. Protocols for studies not submitted initially in the IND should be submitted as a protocol amendment in a future IND serial submission. As noted in the discussion of phase 1 INDs, these protocols may be less detailed and more flexible than protocols for phase 2 and 3 studies. In phases 2 and 3, detailed protocols describing all aspects of the study should be submitted. A protocol for a phase 2 or 3 investigation should be designed in such a way that if the sponsor anticipates that some deviation from the study design may become necessary as the investigation progresses, alternatives or contingencies to provide for such a deviation are built into the protocols at the outset. For example, a protocol for a controlled, short-term study might include a plan for an early crossover of nonresponders to an alternative therapy.

The requirements for a clinical protocol are described in detail in Chap. 8 of this book; however, a brief overview of the protocol content is provided here. A protocol is required to contain the following, with the specific elements and detail of the protocol reflecting the above distinctions depending on the phase of study:

1. A statement of the objectives and purpose of the study.
2. The name and address and a statement of the qualifications (curriculum vitae or other statement of qualifications) of each investigator, and the name of each subinvestigator (e.g., research fellow, resident) working under the supervision of the investigator; the name and address of the research facilities to be used; and the name and address of each reviewing IRB. This information is neatly captured on the form FDA 1572 provided in Figure 2.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
STATEMENT OF INVESTIGATOR
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)
(See instructions on reverse side.)

Form Approved: OMB No. 0910-0014.
Expiration Date: December 31, 1999.
See OMB Statement on Reverse.

NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

1. NAME AND ADDRESS OF INVESTIGATOR

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED.

☐ CURRICULUM VITAE ☐ OTHER STATEMENT OF QUALIFICATIONS

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED.

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES).

6. NAMES OF THE SUBINVESTIGATORS *(e.g., research fellows, residents, associates)* WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S).

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.

FORM FDA 1572 (1/97) PREVIOUS EDITION IS OBSOLETE. **PAGE 1 OF 2**

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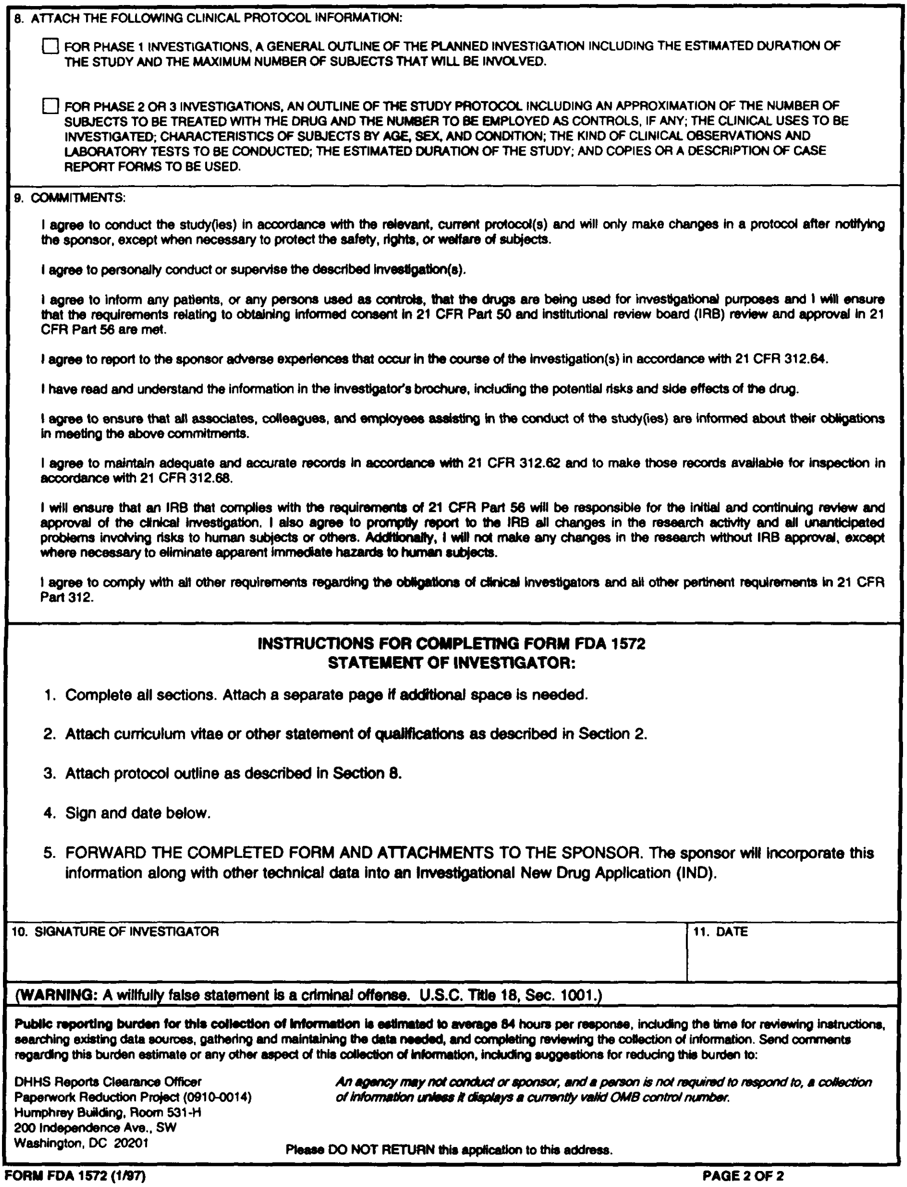
Figure 2. FDA Form 1572.



8. ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION:

☐ FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.

☐ FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMBER TO BE EMPLOYED AS CONTROLS, IF ANY; THE CLINICAL USES TO BE INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY; AND COPIES OR A DESCRIPTION OF CASE REPORT FORMS TO BE USED.

9. COMMITMENTS:

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR:

1. Complete all sections. Attach a separate page if additional space is needed.
2. Attach curriculum vitae or other statement of qualifications as described in Section 2.
3. Attach protocol outline as described in Section 8.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND).

10. SIGNATURE OF INVESTIGATOR	11. DATE

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 84 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS Reports Clearance Officer
Paperwork Reduction Project (0910-0014)
Humphrey Building, Room 531-H
200 Independence Ave., SW
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this application to this address.

FORM FDA 1572 (1/97) **PAGE 2 OF 2**

Figure 2. Continued.

3. The criteria for patient selection and for exclusion of patients and an estimate of the number of patients to be studied.
4. A description of the design of the study, including the kind of control group to be used, if any, and a description of methods to be used to minimize bias on the part of subjects, investigators, and analysts.
5. The method for determining the dose(s) to be administered, the planned maximum dosage, and the duration of individual patient exposure to the drug.
6. A description of the observations and measurements to be made to fulfill the objectives of the study.
7. A description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk.

This section can be best assembled by preparing various subparts. Part 6 (a) will be the complete and signed clinical protocol written in compliance with the above suggestions. Part 6 (b) can be the completed and signed form FDA 1572—Statement of Investigator. A copy of this form is provided in Figure 2. This subpart can also contain the curriculum vitae of the principal investigator. It is up to the discretion of the sponsor as to whether it wishes to file the curricula vitae of all subinvestigators. However, for the sake of minimizing the size of the IND, the FDA is generally in agreement with a statement that all of the curricula vitae of subinvestigators are on file and any or all of the vitae are available upon request. Part 6 (c) is a good place to provide the curricula vitae of the individuals named in items 14 and 15 of the Form FDA 1571, that is, the individual(s) responsible for monitoring the conduct and progress of the clinical investigations and the individual(s) responsible for review and evaluation of information relevant to the safety of the drug.

It should be emphasized that there is no requirement to provide the FDA at the time of the IND submission with copies of a specimen case report form or a specimen informed consent document. However, these are occasionally requested by the agency and should be immediately provided upon request.

Finally, on the introduction page to this section or in the cover letter, it is always a good idea to emphasize that the clinical trial supplies will not be shipped by the sponsor until there is documentation in hand to demonstrate IRB approval, and that the drug will not be shipped to the clinical trial site until after the 30-day review period of the initial IND filing.

Part 7: Chemistry, Manufacturing, and Control Data. This section is also easier to review and better formatted with the use of subparts. Any number of approaches are acceptable; however, one logical formatting technique is to provide the CMC data for the drug substance as subpart (a); data for the drug product as subpart (b); information relating to any placebo formulations as subpart (c); labeling as subpart (d); and finally all environmental assessment information as subpart (e).

The emphasis of this part of the IND is to assure the proper identification, quality, purity, and strength of the investigational drug. As noted earlier in the section on the phase 1 IND, the amount of information needed to make that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available. The FDA recognizes that modifications to the method of preparation of the new drug substance and dosage form and changes in the dosage form itself are likely as the investigation progresses. Therefore, as noted, the emphasis in an initial phase 1 submission should generally be placed on the identification and control of the raw materials and the new drug substance. Final specifications for the drug substance and drug product are not expected until near the end of the investigational process.

Having said this, as drug development proceeds and as the scale or production is changed from the pilot-scale production appropriate for the limited initial clinical investigations to the larger-scale production needed for expanded clinical trials, the sponsor should submit information amendments to update the initial information submitted on the chemistry, manufacturing, and control processes with information appropriate to the expanded scope of the investigation.

At the time of this writing, details on the different levels of data suggested for an IND for the drug substance and drug product may be found in a preliminary draft guidance published by the FDA. The draft guidance is entitled "INDs for Phase 2 and 3 studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products—CMC Content and Format" dated February 1999.

Subpart (a)—Drug Substance: This section will contain a description of the drug substance, including its physical, chemical, or biological characteristics; the name and address of its manufacturer; the general method of preparation of the drug substance; the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug substance; and information sufficient to support stability of the drug substance during the toxicologic studies and the planned clinical studies. Reference to the current edition of the USP-NF may satisfy relevant requirements in this section.

By the time the clinical program has entered phase 3, the sponsor should provide a full description of the physical, chemical, and biological characteristics of the drug substance. For example, most of the following should be evaluated and submitted: solubility and partition coefficient, pKa, hygroscopicity, crystal properties/morphology, thermal evaluation, X-ray diffraction, particle size, melting point, and specific rotation stereochemical consideration. Proof of structure should include information on elemental analysis, conformational analysis, molecular weight determination and spectra for IR, NMR (^{1}H and ^{13}C), UV, MS, optical activity, and single crystal data (if available). For peptides and proteins, amino acid sequence, peptide map, and secondary and tertiary structure information should be available.

For the description of the synthesis or preparation of the drug substance, a detailed flow diagram containing chemical structures (including relevant stereochemical configurations), intermediates (either in situ or isolated), and significant side products, solvents, catalysts, and reagents should be submitted. For biotech or natural products, fermenters, columns, and other equipment/reagents should be identified. By late phase 2 or early phase 3, the synthetic process should be almost completely characterized, and the IND should therefore be able to contain a step-by-step description of the synthesis or manufacturing process, including the final recrystalization of the drug substance. The description should indicate the batch size (range) and descriptions of the types of equipment in which reactions will be carried out. Relative ratios of the reactants, catalysts, and reagents, as well as general operating conditions (time, temperature, pressures), are to be provided. Identification of steps at which all in-process controls are performed (with a complete description of the analytical methods and tentative acceptance criteria to be provided in the Process Control section) is also necessary.

Subparts (b) and (c)—Drug Product and Placebo: These sections require the submission of a list of all components. This may include reasonable alternatives for inactive compounds used in the manufacture of the investigational drug product and placebo, including those components intended to appear in the drug product and those that may not appear but are used in the manufacturing process and, where applicable, the quantitative composition of the investigational drug product, including any reasonable variations that may be expected during the investigational stage; the name and address of the drug product manufacturer and packager; a brief general description of the manufacturing and packaging procedure for the product; the acceptable limits and analytical methods used to ensure the identity, strength, quality, and purity of the drug product; and information sufficient to ensure the product's stability during the planned clinical studies. Reference to the current edition of the USP-NF may satisfy certain requirements in this subpart. There also should be a brief general description of the composition, manufacture, and control of any placebo used in a controlled clinical trial.

By the time the drug product is in phase III, studies should be included to demonstrate the inherent stability of the drug product, and the ability to detect potential degradation products should be available. The analytical method should use a validated stability-indicating assay.

Subpart (d)—Labeling: A copy of all labels and labeling to be provided to each investigator should be submitted in the IND. This would include a mock-up or printed representation of the proposed labeling and labels that will be provided to investigators to be used on the drug container. The investigational labels must also carry the standard "caution statement" as previously discussed.

Subpart (e)—Environmental Analysis Requirements: A claim for categorical exclusion under 21 CFR Section 25.30 or 25.31 or an environmental assessment under 21 CFR Section 25.40 should be provided.

Part 8: Pharmacology and Toxicology Information. This section of the IND must contain adequate information about pharmacologic and toxicologic studies of the drug involving laboratory animals or any studies conducted in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, and scope of animal and other tests required vary with the duration and nature of the proposed clinical investigations. Guidelines are available from the FDA that describe ways in which these requirements may be met. Such information is required to include the identification and qualifications of the individuals who evaluated the results of such studies and concluded that it is reasonably safe to begin the proposed investigations and a statement of where the investigations were conducted and where the records are available for inspection. As drug development proceeds, the sponsor is required to submit informational amendments, as appropriate, with additional information pertinent to safety.

With regard to formatting, this part of the IND may be divided into the following sections: Subpart (a): Pharmacology and Drug Disposition; Subpart (b)(i): Toxicology—Integrated Summary; Subpart (b)(ii): Full Toxicological Reports; and Subpart (c): Good Laboratory Practices Statement.

Subpart (a)—Pharmacology and Drug Disposition: This section should describe the pharmacologic effects and mechanism(s) of action of the drug in animals and information on the absorption, distribution, metabolism, and excretion of the drug, if known.

Subpart (b)(i)—Toxicology: Integrated Summary: An integrated summary of the toxicologic effects of the drug in animals and in vitro should be written. Depending on the nature of the drug and the phase of the investigation, the description is to include the results of acute, subacute, and chronic toxicity tests; tests of the drug's effects on reproduction and the developing fetus; any special toxicity test related to the drug's particular mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology); and any in vitro studies intended to evaluate drug toxicity.

If the drug is to be studied in females of child-bearing potential in phase 2, complete investigations of the effect of the drug on fertility and reproductive performance should be a part of the IND submission.

Subpart (b)(ii)—Full Toxicologic Reports: For each toxicology study that is intended primarily to support the safety of the proposed clinical investigation, a full tabulation of data suitable for detailed review should be submitted. The full reports must be quality assured by the QA Unit of the laboratory that conducted the testing.

Subpart (c)—GLP Statement: For each nonclinical laboratory study subject to the GLP regulations under 21 CFR Part 58, a statement that the study was conducted in compliance with the good laboratory practice regulations, or, if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

Part 9: Previous Human Experience. All previous human experience with the drug must be summarized. The information is required to include the following:

Subpart (a): If the investigational drug has been investigated or marketed previously, either in the United States or other countries, detailed information about such experience relevant to the safety of the proposed investigation or to the investigation's rationale should be provided. If the drug has been the subject of controlled trials, detailed information on such trials that is relevant to an assessment of the drug's safety and effectiveness for the proposed investigational use should also be provided. Any published material that is relevant to the safety of the proposed investigation or to an assessment of the drug's effectiveness for its proposed investigational use should be provided in full. Published material that is less directly relevant may be supplied by a bibliography.

Subpart (b): If the drug is a combination of drugs previously investigated or marketed, the information required in the above section should be provided for each active drug component. However, if any component in such a combination is subject to an approved marketing application or is otherwise lawfully marketed in the United States, the sponsor is not required to submit published material concerning that active drug component unless such material relates directly to the proposed investigational use (including publications relevant to component-component interaction).

Subpart (c): If the drug has been marketed outside the United States, a list of the countries in which the drug has been marketed and a list of the countries in which the drug has been withdrawn from marketing for reasons potentially related to safety or effectiveness must be included.

Part 10: Additional Information. This section is necessary in only a small percentage of INDs to provide information on special topics, as listed below.

Drug Dependence and Abuse Potential: If the drug is a psychotropic substance or otherwise has abuse potential, a section describing relevant clinical studies and experience and studies in test animals is to be submitted.

Radioactive Drugs: If the drug is a radioactive drug, sufficient data from animal or human studies to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject are to be submitted. Phase 1 studies of radioactive drugs must include studies that will obtain sufficient data for dosimetry calculations.

Other Information: A brief statement of any other information that would aid evaluation of the proposed clinical investigations with respect to their safety or their design and potential as controlled clinical trials to support marketing of the drug.

c. *Protocol and Information Amendments*

As noted previously, the sponsor is required to wait 30 days after the submission of the IND before clinical investigations with the new drug may be instituted. Once the IND is in effect, all additional data and information submitted to that IND will be provided in the form of Protocol and Information Amendments, provided as sequentially numbered serial submissions.

Protocol Amendments. It is the obligation of the sponsor to amend the IND to ensure that the clinical investigations are conducted according to protocols included in the IND application. This section will describe the provisions under which new protocols may be submitted and the changes in previously submitted protocols that may be made.

New Protocol: Whenever a sponsor intends to conduct a study that is not covered by a protocol already contained in the IND, the sponsor shall submit to the FDA a protocol amendment containing the protocol for the study. Such a study may begin without delay provided two conditions are met: (a) the sponsor has submitted the protocol to FDA for its review, and (b) the protocol has been approved by the IRB with responsibility for review and approval of the study.

Changes in a Protocol: A sponsor shall submit a protocol amendment describing any change in a phase 1 protocol that significantly affects the safety of subjects or any change in a phase 2 or 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of changes requiring an amendment under this paragraph include:

1. Any increase in drug dosage or duration of exposure of individual subjects to the drug beyond that in the current protocol or any significant increase in the number of subjects under study
2. Any significant change in the design of a protocol (such as the addition or deletion of a control group)
3. The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event or the deletion of a test intended to monitor safety

New Investigator: A sponsor shall submit a protocol amendment when a new investigator is added to carry out a previously submitted protocol. Once the investigator is added to the study, the investigational drug may be shipped to the investigator, and the investigator may begin participating in the study.

The sponsor shall notify the FDA of the new investigator within 30 days of the investigator's being added.

It is important to note the distinction in timing of submissions to the IND for a protocol amendment and the addition of a new investigator. A sponsor must submit a protocol amendment for a new protocol or a change in protocol *before* its implementation. Protocol amendments to add a new investigator or to provide additional information about investigators may be grouped and submitted at 30-day intervals. When several submissions of new protocols or protocol changes are anticipated during a short period, the sponsor is encouraged, to the extent feasible, to include these all in a single submission.

Information Amendments. A sponsor shall report in an information amendment essential information on the IND that is not within the scope of a protocol amendment, IND safety reports, or annual report. Examples of information or data requiring an information amendment include: new toxicology, chemistry, or other technical information or a report regarding the discontinuance of a clinical investigation. Information amendments to the IND should be submitted as necessary but, to the extent feasible, not more than every 30 days.

d. IND Safety Reports

Effective April 6, 1998, the FDA changed definitions associated with adverse experience reporting and the time frame for when IND safety reports must be provided to the FDA in relation to their occurrence.

At present, the following definitions of terms apply to this section:

Associated with the use of the drug means that there is a reasonable possibility that the experience may have been caused by the drug.

Disability. A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse drug experience means any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse drug experience means any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. An example would be blood dyscrasias or convulsions that do not result in in-patient hospitalization.

Unexpected adverse drug experience means any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the product.

Review of safety information. An IND sponsor must review all information relevant to the safety of the drug obtained from any source, foreign or domestic, including information derived from any clinical or epidemiological investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not already been previously reported to the FDA by the sponsor.

There are two types of IND safety reports, written and telephone/facsimile reports. A written IND safety report is required for any adverse experience associated with the use of the drug that is both serious and unexpected; or for any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity. A telephone/facsimile report is required for any unexpected fatal or life-threatening experience associated with the use of the drug. The written report should be made as soon as possible but in no event later than 15 calendar days after the sponsor's initial receipt of the information. The report must clearly indicate the contents as an "IND Safety Report." A telephone/facsimile report must occur not more than 7 calendar days after receipt of the initial information. Any follow-up information obtained after initial notification must be submitted as soon as the relevant information is available.

In the written IND safety report, the sponsor shall identify all safety reports previously filed with the IND concerning a similar adverse experience, and provide an analysis of the significance of the adverse experience in light of the previous, similar reports.

FDA offers the opportunity for the sponsor to make a disclaimer to each IND safety report. The letter of transmittal of the initial and any follow-up reports should state that the information submitted does not necessarily reflect a conclusion by the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse experience. A sponsor need not admit, and may deny, that the report or information submitted by the sponsor constitutes an admission that the drug caused or contributed to an adverse experience.

e. Annual Reports

In order to keep the FDA up to date with the progress of the IND, all sponsors are required to provide an annual report to the IND review division. This must be done within 2 months of the anniversary date that the IND went into effect. The annual report should be brief but summarize the progress of the investigations with the new drug.

This section will describe the information required for an annual report.

For each individual study, it is necessary to provide a brief summary of the status of each investigation in progress and each study completed during the previous year. The summary is required to include the following information for each study:

1. The title and protocol number of the study, its purpose, a brief statement identifying the patient population, and a statement as to whether the study is completed.

2. The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, *tabulated by age group, sex, and race*; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason; the requirement for tabulation by age, group, sex, and race is a new annual report requirement effective February 1998.

3. If the study has been completed or if interim results are known, a brief description of any available study results.

The annual report will also contain summary information obtained during the previous year's clinical and nonclinical investigations including:

1. A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system
2. A summary of all IND safety reports submitted during the past year
3. A list of subjects who died during participation in the investigation, with the cause of death for each subject
4. A list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be drug related
5. A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, controlled trials, and bioavailability
6. A list of the preclinical studies (including animal studies) completed

or in progress during the past year and a summary of the major preclinical findings

7. A summary of any significant manufacturing or microbiological changes made during the past year

A description of the general investigational plan for the coming year to replace that submitted 1 year earlier should be submitted, as well as any revised Investigator's Brochure. If the drug is in phase 1, a description of any significant phase 1 protocol modifications made during the previous year and not previously reported to the IND in a protocol amendment should be identified. If applicable, a brief summary of significant foreign marketing developments with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country, is to be submitted. Finally, if desired by the sponsor, a log of any outstanding business with respect to the IND for which the sponsor requests or expects a reply, comment, or meeting may be included.

f. Clinical Holds and Withdrawal of an IND

The last thing a regulatory professional wants to receive from the FDA is the notification that, for one or more reasons, the IND has been placed on "clinical hold." When this occurs, a sponsor is not allowed to initiate or continue the clinical trial until the FDA has responded in writing that the clinical hold has been removed and the research program may begin. Thus, a clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. The clinical hold order may apply to one or more of the investigations covered by an IND. When a proposed study is placed on clinical hold, subjects may not be given the investigational drug. When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and placed on the investigational drug; patients already in the study should be taken off therapy involving the investigational drug unless specifically permitted by the FDA in the interest of patient safety.

Typically, a clinical hold is imposed prior to a phase 1 investigation if the FDA believes that human subjects are or would be exposed to an unreasonable and significant risk of illness or injury; if the clinical investigators named in the IND are not qualified by reason of their scientific training and experience to conduct the investigation described in the IND; if the Investigator's Brochure is misleading, erroneous, or materially incomplete; or if the IND does not contain sufficient information to assess the risks to subjects of the proposed studies. A clinical hold may occur during phases 2 or 3 for any of these reasons or if the FDA believes the plan or protocol for the investigation is clearly deficient in design to meet its stated objectives.

Details on the FDA's policy for the IND process and review procedures, including the handling of clinical holds, is presented in the FDA Manual of

Policies and Procedures MAPP No. 6030.1, dated May 1, 1998. This document provides the general review principles for investigational new drugs, policies, and procedures for issuing and overseeing clinical holds of INDs and policies and procedures for processing and responding to sponsors' complete responses to clinical holds.

With regard to withdrawal of an IND, this may be done at any time by a sponsor without prejudice. If a decision is taken to withdraw an IND, the FDA shall be notified in writing of this decision, all clinical investigations conducted under the IND shall be ended, all current investigators notified, and all stocks of the drug returned to the sponsor or otherwise disposed of at the request of the sponsor. If an IND is withdrawn for safety reasons, the sponsor shall promptly inform the FDA, all participating investigators, and all reviewing IRBs of the reasons for such withdrawal.

III. THE INVESTIGATOR'S BROCHURE

A. Introduction

The Investigator's Brochure (IB) is an important document, not only required as a part of the IND, but also prepared for presentation to potential clinical investigators and ultimately for presentation to the investigator's IRB. The IB is a compilation of the clinical and nonclinical data on the investigational product that are relevant to the study of the product in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and nonpromotional form that enables a clinician or potential investigator to understand it and make his or her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

The Efficacy Committee of the International Conference on Harmonization has prepared a final guidance (E6) entitled: *Good Clinical Practice: Consolidated Guideline*. This document was issued by the FDA in April 1996, by both the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research. This document should be consulted prior to completion of the final IB.

It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. In this situation, a basic product information brochure, package insert, or labeling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new indication, an IB specific to that new use should be prepared.

The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. The revised version should be included in the IND annual report. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with GCP, relevant new information may be so important that it should be communicated to the investigators, and possibly to the IRBs and the FDA, before it is included in a revised IB.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s), and the investigators are responsible for providing the up-to-date IB to the responsible IRBs.

The following provides the information that should be included in the IB:

1. *Title Page*

This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number and a reference to the number and date of the edition it supersedes be provided.

TITLE PAGE OF INVESTIGATOR'S BROCHURE (Example)

Sponsor's Name:
Product:
Research Number:
Name(s): Chemical, Generic (if approved)
  Trade Name(s) (if legally permissible and desired by the sponsor)
Edition Number:
Release Date:
Replaces Previous Edition Number:
Date:

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2. *Confidentiality Statement*

The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC.

3. *Contents of the Investigator's Brochure*

The IB should contain the following sections, each with literature references where appropriate:

a. Table of Contents

An example of the Table of Contents is given below:

TABLE OF CONTENTS OF INVESTIGATOR'S BROCHURE (Example)

Confidentiality Statement (optional)
Signature Page (optional)
1. Table of Contents
2. Summary
3. Introduction
4. Physical, Chemical, and Pharmaceutical Properties and Formulation
5. Nonclinical Studies
    - 5.1 Nonclinical Pharmacology
    - 5.2 Pharmacokinetics and Product Metabolism in Animals
    - 5.3 Toxicology
6. Effects in Humans
    - 6.1 Pharmacokinetics and Product Metabolism in Humans
    - 6.2 Safety and Efficacy
    - 6.3 Marketing Experience
7. Summary of Data and Guidance for the Investigator

    NB: References on:
    1. Publications
    2. Reports

    (These references should be found at the end of each chapter.)

    Appendices (if any)

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b. Summary

A brief summary (preferably not more than 2 pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacologic, toxicologic, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

c. *Introduction*

A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product(s) pharmacologic class and its expected position within this class (e.g., advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

d. *Physical, Chemical, and Pharmaceutical Properties and Formulation*

A description should be provided of the investigational product substance(s) including the chemical and structural formula(e), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.

To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) also should be given. Any structural similarities to other known compounds should be mentioned.

e. *Nonclinical Studies*

The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavorable and unintended effects in humans.

The information provided may include the following, as appropriate, if known or available:

Species tested
Number and sex of animals in each group
Unit dose (e.g., milligram/kilogram [mg/kg])
Dose interval
Route of administration
Duration of dosing
Information on systemic distribution
Duration of post-exposure follow-up
Results, including the following aspects:
  –Nature and frequency of pharmacological or toxic effects
  –Severity or intensity of pharmacological or toxic effects
  –Time to onset of effects
  –Reversibility of effects

–Duration of effects
–Dose response

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

Nonclinical Pharmacology. A summary of the pharmacologic aspects of the investigational product and, where appropriate, its significant metabolites studied in animals should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g., efficacy models, receptor binding, and specificity), as well as those that assess safety (such as special studies to assess pharmacologic actions other than the intended therapeutic effect(s)).

Pharmacokinetics and Product Metabolism in Animals. A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacologic and toxicologic findings in animal species.

Toxicology. A summary of the toxicologic effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

Single dose
Repeated dose
Carcinogenicity
Special studies (such as, irritancy and sensitization)
Reproductive toxicity
Genotoxicity (mutagenicity)

f. Effects in Humans

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacologic activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results from any use of the investigational product(s) other than in clinical trials, such as from experience during marketing.

Pharmacokinetics and Product Metabolism in Humans. A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:

1. Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination)
2. Bioavailability of the investigational product (absolute, where possible, or relative) using a reference dosage form
3. Population subgroups (e.g., sex, age, and impaired organ function)
4. Interactions (such as, product-product interactions and effects of food)
5. Other pharmacokinetic data (e.g., results of population studies performed within clinical trial[s]).

Safety and Efficacy. A summary of information should be provided about the investigational product's safety (including metabolites, where appropriate), pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product.

Marketing Experience. The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarized (such as, formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

g. *Summary of Data and Guidance for the Investigator*

This section should provide an overall discussion of the nonclinical and clinical data and should summarize the information from various sources on different aspects of the investigational product, wherever possible. In this way, the investigator can be given the most informative interpretation of the available data, with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacologic, toxicologic, and clinical information on the investigational product. Guidance should also be given to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions, based on previous human experience and on the pharmacology of the investigational product.

CONCLUSIONS

This chapter has been prepared to describe in some detail the requirements of an IND application. Emphasis has been placed on the different requirements for the study of a drug in a phase 1 situation compared with a more advanced stage of drug research, that is, phases 2 and 3. Information relating to the submission of IND protocol and information amendments and IND annual reports has also been included. Finally, the newest guidance relating to the writing and content for an IB based on the International Conference on Harmonization has also been provided in detail.

4

General Considerations of the NDA

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I. INTRODUCTION

An NDA is an application submitted to the United States FDA for permission to market a new drug product in the United States. The content of an NDA is designed to answer several questions: Does the new product provide a proven medical benefit? Are the associated risks acceptable compared to the benefits? Can the product be manufactured reproducibly and reliably? Are the data in the NDA reliable?

Since 1963, all new drug products introduced into commerce in the United States have been the subjects of NDAs approved by the FDA, with some exceptions. For the approval of vaccines, traditional biological products (such as blood fractions), and genetically-engineered biotechnical products, BLAs are used. Biologics license applications answer the same questions as NDAs about medical benefit, acceptable risks, and reliability of manufacturing and data. Generic drug products, which are designed to be equivalent to products already on the market, are subjects of ANDAs. An ANDA is designed to provide data that show the new product to be equivalent to the existing product, the method of manufacture to be reliable, and the information in the ANDA to be reliable. However, an NDA is needed if the route of administration is changed for a previously approved drug. For example, if the proposed product is a nasal spray and the previous product was an orally administered tablet, an NDA is needed.

With the increasingly sophisticated technology now available, there is a growing number of products that are combinations of drugs and devices. In these drug-device combinations, both the drug and the device may contribute to medical benefit. At present, the FDA is evaluating these drug-device combinations on a case-by-case basis to determine whether the product should be classified as a drug or device. It is recommended that the manufacturer obtain a classification as a drug or device from the FDA as early in development of the drug-device combination as possible.

The format and content of the documents in an NDA and the administrative actions associated with an NDA continue to evolve. In the last 10 years, the NDA process has been affected by increasing globalization, serious incidences of fraud and graft, the AIDS epidemic, increased ease and speed of electronic data transfer, and greater accountability within the executive branch of the government. One example of the result of these forces was the implementation of user fees and the significant shortening of the review times by the FDA.

II. REGULATIONS, FORMS, AND GUIDANCES

The forms, regulations, and guidelines needed for assembling an NDA are available from the FDA's website on the internet, www.fda.gov. On that website, the section for human drugs, which is maintained by CDER, is the most useful because NDAs for new drugs are reviewed by CDER. Alternatively, Title 21 of the Code of Federal Regulations (21 CFR) can be purchased from government bookstores located in major cities or from the Government Printing Office. Copies of the various guidelines are available from the FDA Drug Information Branch, HFD-210, 5600 Fishers Lane, Rockville, MD 20857; phone (301) 827-4573.

The form to use for either an NDA, a BLA or an ANDA is Form FDA 356h, "Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use." The form requests the name, address, phone and fax numbers of the applicant or owner of the NDA. If the applicant is a foreign corporation or other entity, it is necessary to list an agent in the United States with legal authority to represent the foreign applicant. Product information such as the generic name, chemical or biochemical name, dosage form, strengths, route of administration, and proposed indications for use are to be entered on the form. For new drugs, a name approved by USAN is needed. Another form, Form FDA 3397, the User Fee Cover Sheet, is needed for inclusion in the NDA in addition to Form FDA 356h.

The regulations governing NDAs for new drugs are in 21 CFR Part 314, and those for biologics are in 21 CFR Part 601. These describe the format and content of an NDA and also the legal and administrative procedures connected with an NDA. The regulations describing the bioavailability and bioequivalency testing needed for approval of an NDA are in 21 CFR Part 320. The proposed labeling for the new drug needs to be included in the NDA, and 21 CFR Part 201 contains these regulations. The manufacturing facilities for the new drug product and for the active pharmaceutical ingredient (API) need to be in compliance with GMP regulations, 21 CFR Parts 210 and 211. For nonclinical safety studies, the GLP regulations are in 21 CFR Part 58. For clinical studies in the NDA, the applicable regulations are those for informed consent, 21 CFR Part 50, IRBs, 21 CFR Part 56, the Declaration of Helsinki, 21 CFR Part 312.120, INDs, 21 CFR Part 312, and financial disclosure by clinical investigators, 21 CFR Part 54. An NDA also requires an environmental impact statement covering the manufacture of the proposed product. The regulations covering this are in 21 CFR Part 25.

The FDA has issued a series of guidance documents for the preparation and assembly of the technical sections and summary for the NDA (1–13). A complete list of available guidance documents issued by CDER is on the Internet at www.fda.gov/cder/guidance/index.htm. These guidance documents are also available through the fax-on-demand service that the FDA maintains (phone 800-342-2722 or 301-827-0577). Guidelines do not have the same force as regulations, thus it is not absolutely necessary to follow them. However, it is recommended that guidelines be followed, if possible. If there is a deviation from a guideline, a clear explanation of the reason for the deviation should be provided.

The FDA has issued specifications for the color-coded binders that are needed for the volumes of an NDA. The binders can be ordered from the U.S. Government Printing Office, Washington, DC 20404-0001 (phone 202-512-1800). Alternatively, applicants can have the binders made and printed according to the FDA specifications. The specifications for binders for NDAs, include specifications IND and Drug Master Files binders, can be found on the Internet at www.fda.gov/cder/ddms/binders.htm. The binders have been assigned form numbers, FDA Form 2626 and FDA Forms 2626a through h. These numbers are useful for ordering from the Government Printing Office.

III. SECTIONS OF AN NDA

In addition to Form FDA 356h, an NDA contains an index, a summary, five or six technical sections, tabulations of clinical data and case report forms, and patent information and various certifications. Safety update reports submitted after the initial filing are also considered part of an NDA.

The index should be comprehensive, with the volume number and page number indicated for the sections of the summary, the individual technical reports, the tabulations of clinical data by study, the case report forms, and any other information or certifications. It is also advisable to have indices for each technical section and volume.

The summary should provide each FDA reviewer an overview of the entire NDA. It should be organized according to the guidance document (1), and should be written at approximately the level of detail used for publications in scientific and medical journals. Whenever possible, the data should be presented using tables and figures. Electronic copies of the each of the technical sections of the summary are submitted to the FDA reviewers for use in preparing the assessments needed for approval. The assessments from the FDA reviewers are subject to public disclosure after approval of the NDA.

Included in the summary is a discussion of the scientific basis for the proposed clinical use and the possible benefits of the drug, which sets the stage for the rest of the NDA. It should be focused and should logically present the reasons why approval of the drug would benefit both patients and the medical community.

Also included with the summary is the annotated package insert. This document contains the labeling that the applicant wishes to use with the commercial product. The advertising material will eventually be based on the statements in this insert. In annotating the package insert, each statement should have a reference to a document or report within the NDA. However, some drugs may need to include sections known as "class labeling," which are statements regarding the pharmacologic class of the drug that have been issued by the FDA, based on information on other drugs in the same pharmacologic class. The FDA regulations for labeling specify the format for the package insert (21 CFR Part 201.57). If any sections listed in the labeling regulations are excluded from the insert, an explanation of the omission should be included with the annotated package insert. During review of the NDA, each statement will be scrutinized word-by-word to assure that there is sufficient documentation for each of the statements and that the risks of the drug are adequately presented.

The technical sections of an NDA are (a) the chemistry section consisting of the chemistry, manufacturing, and controls information (2,4–6,8), the methods validation package (7), and reference samples of drug, possible impurities, and drug product (7); (b) the nonclinical pharmacology and toxicology section, which includes the drug metabolism and animal pharmacokinetic information (12); (c) the human pharmacokinetics and bioavailability section (11); (d) the microbiology section (3); (e) the clinical data section (9); and (f) the statistical section (9). Other chapters in this book discuss the types of studies needed for these technical sections. Although the regulations and guidance documents indicate that a microbiology section is required only for antimicrobial drugs, this is not strictly observed. Microbiology sections have been requested for topical products (for evaluation of the possible microbial load in the product) and for a product whose primary mechanism of action was not antimicrobial, but that did have auxiliary antimicrobial activity in animals and in vitro. It would be wise to check with the reviewing division of the FDA to determine whether a microbiology section is necessary.

Following the technical sections in an NDA, the regulations request tabulations of the data from the case report forms for most of the clinical studies. Usually, these tabulations are part of the report for each clinical study and are included in the technical sections. If the tabulations are not included with the reports of the clinical studies, they should be indexed and combined in this section of the NDA. Whether the tabulations are with the reports or in a separate section, complete listings of all data (demographic, safety, efficacy, etc.) should be included for each controlled phase 2 and phase 3 study and for the phase 1 studies. If there are other studies supporting the NDA, listings of the safety data from these studies need to be included.

The regulations request that the NDA contain copies of the complete case report forms for any patient who died during a clinical study or who withdrew due to an adverse event. The FDA may not require the case report forms if they are considered unnecessary for a review of the NDA. On the other hand, the FDA may request copies of case report forms for other patients, such as all those who did not complete the studies, regardless of cause. This should be discussed with the reviewing division before the NDA is prepared.

Information on United States patents related to the drug or drug product is to be included in the NDA. The relevant types of patents are the composition-of-matter patent for the API, patents related to the formulation or composition of the drug product, and use patents that are applicable to the clinical indications claimed in the NDA. Process patents for any of the manufacturing processes used for the API or drug product need not be included. The applicant must certify the validity of each patent listed in the NDA. The proper wording for these certifications is in the regulations (21 CFR Part 314).

A variety of items within an NDA serve as assurance that the information in the application is correct and reliable. Each nonclinical toxicology or safety study should have a QA statement indicating compliance with the GLP regulations. If a laboratory conducting one or more of the studies has not provided a QA statement in the report, the NDA should explain the omission. In current general practice by pharmaceutical firms and contract laboratories, GLP regulations are also applied to the analysis of the drug in plasma, serum, or urine samples from clinical studies.

For each clinical study, there should be statements that the study was conducted in compliance with the informed consent regulations and either the IRB regulations or the Declaration of Helsinki. If any obligations for the conduct of the study were transferred to a CRO, the name and address of the CRO and the obligations transferred should be listed in the NDA. The clinical sites audited or monitored by the sponsor should be identified, either as part of the report for the study or as a separate list.

For each clinical investigator, the NDA should include either a certification that the investigator did not have any financial interests that could be considered to be a conflict of interest, or a disclosure of the financial interests.

Financial interests that are considered a possible source of bias according to the regulations (21 CFR Part 54) are (a) compensation based on a favorable outcome of the study, such as royalty payments or other payments based on the sales of the product, (b) significant equity interest in a company that is not publicly traded or equity valued at more than $50,000 in a publicly traded corporation, (c) proprietary interest in the product such as a patent or licensing agreement, and (d) payments during the study or 1 year after the study of more than $25,000 above the costs of the study. The last condition applies to both the investigator and the affiliated institution. Payments considered in excess of the costs of the study include such things as funds for research, equipment, consulting retainers, and honoraria.

The reliability of the chemistry, manufacturing, and controls information in the NDA is checked by review of the documents, inspection of the manufacturing facilities, and analysis of the API and drug product in the FDA laboratories. The facilities used for the manufacture of the API and of the drug product will be inspected for compliance with GMP regulations. If the facilities have been used previously for the production of marketed drugs in the United States, reports of biannual inspections will be on file at the FDA. Some time after the original submission of the NDA, the applicant will receive a request from the FDA to send to the FDA laboratory a copy of the methods validation package and samples of the API, drug product, and reference standards for the drug and its impurities. A form FDA 356h, indicating an amendment to a pending application, should accompany the methods validation package and samples.

Because of instances of fraud, the FDA has instituted procedures for the debarment of individuals. An NDA needs to contain a certification that the applicant has not and will not use the services of any debarred individual in any capacity (14). Notices of the debarment of individuals are published in the Federal Register. The current debarment list is available from the FDA internet site or from the Division of Compliance Policy. Note that the certification includes the statement that the applicant will not use any debarred person in the future. Thus, it is recommended that the list be checked periodically, especially before letting any contracts. The FDA has been interpreting the phrase "in any capacity" to include jobs that are not involved with drug development, such as landscaper or accountant.

IV. NDA REVIEW PROCESS

Before an NDA is submitted to the FDA, the applicant usually meets with the reviewing division in a pre-NDA meeting. The applicant presents a summary of the clinical studies, the proposed format for the organization of the NDA, and any other information the applicant considers relevant. The purpose of the meeting is to uncover any major unresolved issues and to help the reviewers become acquainted with the information to be included in the NDA. By this time, the classification of the NDA will be known to both the FDA and the applicant. The Center for Drug Evaluation and Research classifies NDAs with a number indicating the type of product and a letter indicating the priority of the review. The types of drugs are as follows:

1. New molecular entity
2. New salt of previously approved drug
3. New formulation of previously approved drug
4. New combination of two or more drugs
5. Already marketed drug product—duplication by new manufacturer
6. New indication for already marketed drug, including switch in status to OTC
7. Already marketed drug product without previously approved NDA

The codes for the priority of the review are as follows:

S Standard review for drugs similar to currently available drugs
P Priority review for drugs that represent significant advances over existing treatments

Upon receipt of an NDA, the FDA conducts a review of the application to determine its completeness. Within 60 days, the FDA either accepts the filing or sends the applicant a "refusal-to-file" letter. If the applicant receives a refusal-to-file letter, they can request a conference with the FDA. Grounds for refusing to file the application include:

Form FDA 356h has not been completed.
The format of the application is not correct (21 CFR Part 314.50).
One or more items is missing from the content as described in the regulations (21 CFR Part 314.50).
The manufacturing facilities are not ready for inspection.
The environmental assessment is incomplete or there is insufficient information for consideration of a waiver.
Complete and accurate translations of all parts of the application not in English are not included.
There are no statements regarding GLP compliance for each of the nonclinical studies.
There are no statements regarding compliance with IRB and informed consent regulations for each of the clinical studies.
The drug product is already covered by an approved NDA or ANDA.

After the NDA is accepted for filing, the various sections undergo concurrent review. The clinical information is reviewed by a medical officer, usually a physician. The nonclinical information on pharmacology, toxicology, and drug metabolism is reviewed by a pharmacologist. The information on the chemistry, manufacturing, and controls for both the API and the drug product are reviewed by a chemist. A statistician evaluates the relevance of the statistical methodology used and provides the medical officer with an assessment of the power of the findings and their extrapolation to the entire patient population. For an anti-infective drug, a microbiologist will review the effect of the drug on the target microorganisms and will assess any microbiology tests that may be needed for clinical isolates. The biopharmaceutics section is reviewed by a pharmacokineticist who determines if there is sufficient information on the metabolism and elimination of the drug, and if the bioavailability and bioequivalency studies support the clinical data and the dissolution specifications. The medical officer takes the lead in integrating the results of the findings of the other reviewers with the clinical information.

When easily correctable deficiencies are found during the review, the FDA will notify the applicant, usually by phone or fax, and the applicant should send the additional information as soon as possible. At the end of the review, there may be more substantial scientific or medical issues, which would be discussed with the applicant and may also be presented to an advisory committee. An advisory committee for a division of the FDA includes medical experts in the therapeutic area and other relevant experts such as a statistician. The opinions of an advisory committee are not binding on the FDA; however, the FDA is very unlikely to override a negative advisory committee opinion. If scientific and medical issues remain after both discussions and an advisory committee, the FDA may request that additional information or revisions be submitted as an amendment to the NDA (15).

The applicant will be asked to submit safety reports 4 months after the initial submission and at other times requested by the FDA (21 CFR Part 314.50). These safety reports will include any animal or clinical safety data that were not available at the time of the initial submission.

When the scientific and medical issues are resolved, the CDER reviewing division will verify that the inspections of the manufacturing sites and selected clinical sites were satisfactory. Based on the medical and scientific reviews, the proposed labeling for the drug product will be reviewed. At this stage, the FDA will send one of three possible action letters to the applicant. One possibility is a "Not Approvable Letter," which will list the deficiencies in the NDA and explain why it cannot be approved (21 CFR Part 314.120). The second possibility is an "Approvable Letter," which indicates that ultimately the drug product should be approved, but lists minor deficiencies and labeling changes that are needed before approval (21 CFR Part 314.110). Requests for commitments for post-approval studies may be included. The third possibility is an "Approval

Letter" (21 CFR Part 314.105). An applicant may receive both an Approvable Letter and an Approval Letter.

V. APPROVAL TIMES

Since the implementation of the PDUFA, the review times for NDAs for new molecular entities have dropped dramatically. In 1993, the median total approval time was 23 months, of which 21 months were used by the FDA, and 25 new molecular entities were approved. By 1996, the median time had dropped to 14.3 months for total time, with a median of 12 months for FDA review, and 53 new entities were approved. Similar reductions in review time and increases in numbers of NDAs reviewed have also occurred for supplements for manufacturing changes and for new clinical indications (16).

The reduction in review time and increase in number of approvals have been the result of increased efforts and efficiency at the FDA and the preparation of better NDAs by pharmaceutical companies. Better communication between the FDA and applicants has also contributed to the improvement. In 1993, 26% of the 113 original NDAs were rejected by the FDA during the initial review for completeness. By 1997, the percentage of refuse-to-file actions had decreased to 1.6% for 124 original applications. These efficiencies have also spilled over into the IND arena, resulting in a lower percentage of clinical holds on a higher number of INDs received (16).

In conclusion, the review and approval process for NDAs for new drugs is much more efficient than in the past. To take advantage of the efficiency of the FDA, the applicant should prepare the NDA carefully, making sure all the necessary information is present. In addition, the applicant should be aware of the various certifications and statements that will be needed in an NDA when they choose contractors and clinical investigators.

REFERENCES

1. Format and Content of the Summary for New Drug and Antibiotic Applications. Guidance for Industry. Food and Drug Administration. February 1, 1987.
2. Format and Content of the Chemistry, Manufacturing and Controls Section of an Application. Guidance for Industry. Food and Drug Administration. February 1, 1987.
3. Format and Content of the Microbiology Section of an Application. Guidance for Industry. Food and Drug Administration. February 1, 1987.
4. Submitting Documentation for Packaging for Human Drugs and Biologics. Guidance for Industry. Food and Drug Administration. February 1, 1987.

5. Submitting Documentation for the Manufacturing of and Controls for Drug Products. Guidance for Industry. Food and Drug Administration. February 1, 1987.
6. Submitting Documentation for the Stability of Human Drugs and Biologics. Guidance for Industry. Food and Drug Administration. February 1, 1987.
7. Submitting Samples and Analytical Data for Methods Validation. Guidance for Industry. Food and Drug Administration. February 1, 1987.
8. Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances. Guidance for Industry. Food and Drug Administration. February 1, 1987.
9. Format and Content of the Clinical and Statistical Sections of an Application. Guidance for Industry. Food and Drug Administration. July 1, 1988.
10. Formatting, Assembling and Submitting New Drug and Antibiotic Applications. Guidance for Industry. Food and Drug Administration. February 1, 1987.
11. Format and Content of the Human Pharmacokinetics and Bioavailability Section of an Application. Guidance for Industry. Food and Drug Administration. February 1, 1987.
12. Format and Content of the Nonclinical Pharmacology/Toxicology Section of an Application. Guidance for Industry. Food and Drug Administration. February 1, 1987.
13. Submitting Supporting Chemistry Documentation in Radiopharmaceutical Drug Applications. Guidance for Industry. Food and Drug Administration. November 1, 1991.
14. Draft Guidance. Submitting Debarment Certification Statements. Food and Drug Administration. September, 1998.
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16. CDER 1997 Report to the Nation, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. May 1, 1998.

5

Specific Requirements, Content, and Format of an NDA

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I. INTRODUCTION

When an NDA is submitted to the FDA, it must be carefully prepared and well indexed as well as comprehensive and readable. The guidelines issued by the FDA provide proper formats for pharmaceutical manufacturers to follow. This section will describe the specifics needed to format, assemble, and submit an NDA. It is the applicant's responsibility to submit data that will satisfy the requirements of the Food, Drug, and Cosmetic Act and the regulations used by the FDA in the review and approval of safe and effective drug products.

As one plans the formatting, there must be a clear understanding of how to separate the most frequently needed data from the supporting material. The FDA guidelines and meetings with the FDA, particularly the pre-NDA submission conference, is invaluable to the applicant, especially if unforeseen problems arise owing to the nature of the product or data.

A brief description of each specific section in the Code of Federal Regulations, Title 21, Section 314 (21 CFR 314) will help identify the purpose of the item, particularly for those with no prior knowledge of the format and content of an NDA. The specific components will be described and commented upon, and suggestions on how to package the submission will be presented.

II. CONTENT AND FORMAT OF AN APPLICATION

All applications, including abbreviated applications and supplements to approved applications, must be formally submitted (as appropriate for the particular submission) and to contain the information required in 21 CFR 314.50. Two copies of the application are needed: an archival and a review copy. An application for a new chemical entity will generally contain a signed FDA 356h form, an index, a summary, five or six technical sections, case report tabulations of patient data, case report forms, drug samples, and labeling. Abbreviated applications and supplements to applications usually contain only some of the above items, and information will be limited to what is needed to support the particular application.

III. FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS

With the development of new NDA regulations implemented in 1985 to improve the NDA process, the FDA designed an application format more amenable to efficient review (1). The changes included requiring fewer copies (two as opposed to the previously required three) of the NDA, allowing a parallel review of all the technical data, eliminating the need for submission of all case report forms (except in certain cases), and permitting submission of certain segments on microfiche. It is expected that the previously large submissions will be cut down considerably, thereby improving review time and, it is hoped, resulting in more approvals in a shorter period.

There are no shortcuts in the preparation of an NDA. The items highlighted in this chapter encompass information that can take literally thousands of pages of detailed explanation. To help prevent delays until approval is granted, the sponsor of a new drug must meticulously organize the NDA, check and recheck every fact, explain all omissions, and summarize all relevant information in an accurate, clear, concise, and complete manner. One author, experienced in submitting NDAs, has stated that, "Every NDA is a learning experience. A study that was sophisticated when planned 3 years ago may seem less than adequate when subjected to the harsh glare of tomorrow's advisory committee review" (2). It is of extreme importance for a sponsor to anticipate and minimize time-consuming problems.

A. Application Format

The NDA regulations (21 CFR 314.50) require the submission of an archival copy and a review copy.

1. Archival Copy

This is a complete copy of an application submission and is intended to serve as a reference source for FDA reviewers to locate information not contained in the review copy, as a reference source for other FDA officials, and as the repository of the copies of tabulations and clinical study case report forms.

After approval, the archival copy is retained by the FDA and serves as the sole file copy of the approved application. Certain parts of the archival copy will be accepted on microfiche, another suitable microform system, or by electronic (computer) means.

2. *Review Copy*

The review copy of an application is divided into five (or six) sections containing the technical and scientific information required by FDA reviewers. Each of the technical sections of the review copy is separately bound. With the review copy, each reviewer should be provided with the following:

1. A copy of the cover letter
2. A copy of the application form (FDA 356h)
3. A copy of the overall summary
4. A copy of the index to the entire application
5. An index to the specific review section

B. Assembling the Application

1. *Folders*

Because of the procedures used at the FDA to file and retrieve material from the document rooms where applications are kept, it is necessary that applicants use the colored folders (or "jackets") to bind the archival copy and each technical section. The folder colors and form numbers are listed below.

Documents	Folder Color	Folder Number
Archival copy	Blue	FD 2626
Chemistry, manufacturing, and controls section	Red	FD 2626a
Nonclinical pharmacology and toxicology section	Yellow	FD 2626b
Human pharmacokinetics and bioavailability section	Orange	FD 2626c
Microbiology section	White	FD 2626d
Clinical data section	Light Brown	FD 2626e
Statistical section	Green	FD 2626f

The cover of each folder should bear the NDA number (if known), the name of the applicant, and the name of the drug product. It should also identify the kind of submission by the heading shown above.

Applicants may purchase these folders from the FDA. Requests should be made on company letterhead, and specify the color(s) of the folder, the FD form number(s), the quantities required, the location where the shipment should be sent, and the name and telephone number of a contact person in case additional information about the order is needed.

2. *Paper Size and Binding*

All applications must be bound on the left side of the page using the United States standard size loose-leaf page (8½″ × 11″).

Both sides of the page may be used for the presentation of information and data, provided:

1. Information and data on both sides are not obscured in the binding
2. Legibility is not impaired because of bleeding of the copy through the page
3. Pages are in correct order and accurately numbered

3. *Pagination*

Any method of pagination may be used, as long as the paging and indexing permit rapid access to the entire submission. It is important that all pages in the application be numbered and that the numbering of the review copy pages be the same as the numbering of the corresponding pages in the archival copy.

If the archival copy is submitted on microfiche, the page numbers on the microfiche page image should correspond to the page numbers in the review copy.

4. *Volume Size and Identification*

Volumes submitted in hard copy form should be no more than 2 inches thick. As previously discussed, the front cover of each volume should have the proper information: name of applicant, drug, and NDA number (if previously assigned), clearly written in waterproof marking pen or on typed, stick-on labels. Preprinted in the lower right-hand corner of each jacket cover is the legend, "THIS SUBMISSION: VOL. ______ OF ______ VOLS." The blanks should be filled in by the applicant to identify the specific volume and the total number of volumes submitted. For example, the first volume of a 50-volume submission would be, "VOL. *1* OF *50* VOLS."

Numbering of the volumes for the technical sections of the review copy should be the same as that used for the volumes of the archival copy.

Preprinted on the upper right-hand corner of each jacket is "VOLUME ____." This section should be filled in for original applications and for chemistry presubmissions only. This section should be filled in with two numbers, the first giving the order in which the submission has been made and the second identifying the specific volume of the total number in that submission.

Microfiche corresponding to more than one volume of the paper (hard copy) application may be bound together if a clear physical separation is made between each "volume" of microfiche. This can be accomplished if one or more empty slots is left between the last microfiche sheet of one volume and the first microfiche sheet of the next. New drug application numbers for applications submitted in microfiche will be preassigned. For more information and details on the use of microfiche, the FDA has prepared a guideline for the submission in microfiche of the archival copy of the application. Contact the Office of Management (HFN-42) at the FDA for this information.

5. *Packing Carton*

The box size of 14″ × 12″ × 9½″ is recommended for shipment of applications to FDA. Because ANDAs are handled and stored separately, smaller boxes may be appropriate for them. An exterior label should indicate the contents by applicant's name, drug name, and volume numbers; it is also important to identify which cartons contain the archival copy and which the review copy.

Full applications should be sent to:

Food and Drug Administration
Office of Drug Evaluation and Review
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Abbreviated applications should be sent to the Division of Generic Drug Products.

6. *Supplements, Amendments, and Postmarketing Reports*

The submission format for amendments to pending applications and supplements to approved applications will be the same as an original application. Each submission will consist of two copies: a complete archival copy and an appropriately segmented review copy.

Amendments, supplements, resubmissions, annual reports, and other correspondence concerning full applications should be addressed to the appropriate FDA reviewing divisions.

Postmarketing reports of adverse drug experience, including the 15-day "alert reports" and the periodic drug experience reports, should be submitted, unbound, in duplicate, to:

Food and Drug Administration
Office of Drug Evaluation and Review
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

C. Application Content

1. *Full Application*

a. Archival Copy

The archival copy should include a cover letter that confirms agreements or understandings between the FDA and the applicant. The letter should cite any relevant correspondence or meetings by date and topic, and identify one or more persons the FDA may contact regarding the application. The letter may include any other important information the applicant wishes to convey to the FDA about the application.

The archival copy is required to contain the following:

Application Form (FDA 356h). The application form, which serves as a cover sheet for the application, contains basic identifying information about the applicant and the drug product. Importantly, it obligates the applicant to comply with applicable laws and regulations. These include GMPs (21 CFR 210 and 211); labeling regulations (21 CFR 201); prescription drug advertising regulations (21 CFR 202); regulations on making changes in an application (21 CFR 314.70, 314.71, and 314.72); regulations on reports (21 CFR 314.80 and 314.81); and local, state, and federal environmental impact laws.

If the person signing the application does not reside or have a place of business within the United States, the application must contain the name and address of, and be countersigned by, an attorney, agent, or other authorized official who resides or maintains a place of business within the United States (many CROs act as the legal agent for foreign pharmaceutical companies not having an established office in the United States).

The application form, as well as the index and the summary (items 1 and 2), should be bound together in a single volume. Items 3 to 12 should be submitted in separately bound volumes in the order in which they are listed. Patent information on the applicant's drug (item 13) and a patent certification with respect to the drug (item 14) should be submitted on a separate piece of paper attached to the application form itself.

All IND applications, DMFs, and other applications that are referenced in the application must be identified in the space provided on the application form. It is recommended that the applicant use the following format:

Type of Document (IND, NDA, DMF)	Document No.	Title or Subject of Document	Document Holder	Vol. Page No., Dates, etc.

An applicant may obtain copies of the application form (FDA 356h) by writing to the following address: Forms and Publication Distribution (HFD-268), 12100 Parklawn Drive, Rockville, Maryland 20852 or by downloading them from the Internet.

Index. The comprehensive index will contain the volume and page number for the summary, the technical sections, and any supporting information. The index serves as a detailed table of contents for the entire application. It is prudent for the sponsor to keep additional copies of the index and have them available if drug regulatory personnel are contacted by a reviewer. If microfiche is used for portions of an application, the fiche number should also be noted.

Each technical review section should have a copy of the overall index and an individualized table of contents based on the relevant portions of the application index.

Summary. This item, covered in the "Guideline for the Format and Content of an Application Summary," will be reviewed later in this chapter.

IV. NDA SUMMARY FORMAT AND CONTENT

The summary should present in a comprehensive way the most important information about the drug product and the conclusions that can be drawn from the presentation. It must reflect a factual review of, and a neutral analysis of, the safety and effectiveness data. The summary should contain an annotated copy of the proposed labeling, a discussion of the benefits and risks of the drug, a discussion of the non-United States marketing history of the drug, and a summary of each technical section. In general, the summary should be as concise as possible—according to the guidelines, from 50–200 pages in length. One should also keep in mind that this will be the most widely distributed portion of the NDA at the FDA and will also serve as the basis for drafting the SBA for the product. The components of the summary are as follows:

A. Annotated Package Insert

This section should include the proposed text of the labeling for the product, with each statement made referenced back to the data in the technical sections that support the statement. For each statement, claim, caution, or related group of statements, the proposed text of the package labeling must be annotated by reference to volume and page number to the information in the summary and in the technical sections of the application in support of the statements. The format of labeling must follow that described in 21 CFR 201.57 and will form the basis for the advertising and promotion of the drug product. The labeling also serves as a minisummary of the NDA, and any omissions must be explained. This applies to information and to any section or subsection of the labeling format.

B. Pharmacologic Class, Scientific Rationale, Intended Use, and Potential Clinical Benefits

A brief statement should be included to identify the pharmacologic class of the drug, the scientific rationale for the drug, its intended use, and its potential clinical benefit(s). Again, the development of the labeling should provide a basis for supplying the above information on the basis of the clinical pharmacology and indications for use.

C. Foreign Marketing History

If the product is marketed outside the United States, regardless of the dosage form, strength, salt, ester, or complex of the drug, the marketing history should be provided. This should include a list of the countries in which the product is marketed, with dates of marketing, if known, and a list of any countries in which the drug has been withdrawn for any reason related to safety or effectiveness. Specific reasons for withdrawal should be given.

D. Chemistry, Manufacturing, and Controls

The chemistry, manufacturing, and controls summary must provide a general overview of the drug substance and the drug product.

1. Drug Substance

Description, including physical and chemical characteristics and stability.

a. Names

Indicate the established (generic) name, synonym(s), code designation(s), proprietary (brand name or trademark) name, identification number (e.g., chemical abstract service (CAS) registry number), and chemical name. The applicant should not designate a drug or ingredient by a proprietary name that, because of a similarity in spelling or pronunciation, may be confused with the proprietary name or the established name of a different drug already available in the United States marketplace.

Note: The FDA discourages the use of fanciful proprietary names for a drug or any ingredient that might imply that the drug or ingredient has some unique effectiveness or composition when, in fact, the drug or ingredient is a common substance, the limitations of which are readily recognized when the drug or ingredient is listed by its established name.

b. Physical and Chemical Characteristics

The physical and chemical properties of the drug substance must be described in detail, including appearance, physical form, solubility, melting and/or boiling points, molecular weight, structural and molecular formulas, and Wisswesser line notation (WLN). Where applicable, provide information on isomers, polymorphs, pKa values, and pH. Include, in brief, the data obtained and reference standard(s) used to elucidate the structure of the drug substance.

c. Stability

Summarize the results of all stability studies. Stability data should be submitted for the drug substance in the container in which it is packaged.

1. Manufacturer. Provide the name and address of the manufacturer, i.e., the person(s) who performs the manufacturing, processing, packaging, labeling, and control operations on the drug substance. If more than one person is involved in any of these operations, describe the responsibilities of each.
2. Method of Manufacture. Describe the methods of synthesis or isolation and purification. Flow charts may be used to present this information.
3. Specifications and Analytical Methods. Describe the acceptance specifications and test methods used to assure the identity, strength, quality, and purity of the drug substance and the bioavailability of the drug products made from the drug substance. Any actual or potential impurities, by-products, and degradation products should be indicated. When test methods and specifications are established by an official compendium or other public standard, cite the standard used.

2. Drug Product

a. Composition and Dosage Form

State the composition: the name and amount of each active and inactive ingredient in the drug product in the form in which it is to be distributed (e.g., amount per tablet). Describe the dosage form: full details as to type and physical characteristics (e.g. shape, color, coating, and hardness).

b. Manufacture

State the name and address of the manufacturer of the drug product. If more than one entity is involved in any part of the process, describe the responsibilities of each. Describe the manufacturing and packaging process for the finished dosage form.

c. Specifications and Analytical Methods

Describe, as with the drug substance, the acceptable specifications for the drug product and the test methods used to assure the specifications. Cite any official compendia.

d. Container/Closure System

Describe the proposed container/closure system(s) in which the drug product is to be marketed. Safety closure systems should be detailed.

e. Stability

State the proposed expiration dating period and storage conditions. Summarize the stability studies justifying the expiration dating period. Stability data should be submitted for the drug product in the container in which it will be marketed.

f. Investigational Formulations

Provide the quantitative composition and lot number of each finished dosage form used in each clinical trial, bioavailability and pharmacokinetic study, clinical pharmacology study, and dose tolerance study conducted during the investigational phases of the drug product. Cross-reference each formulation to the study report in the application and explain any differences in formulation.

E. Nonclinical Pharmacology and Toxicology Summary

In the nonclinical pharmacology and toxicology summary, all applicable studies must be listed. Provide an overview of the data from these studies with emphasis on notable adverse effects and dose relationships, species similarities and differences, and identified mechanisms for effects. The discussion should center on the appropriateness and adequacy of the data in support of the drug's proposed therapeutic uses.

Tabular summaries should be used that permit identification and comparison of the pertinent observations.

It is recommended that the studies for this section be presented as follows:

1. Pharmacology studies. Further subgroup by type of test with studies that support the pharmacologic activity of the drug first, followed by secondary studies and safety pharmacology studies.

2. Acute toxicity studies. Tabulate species, sex, age, dose range, pharmacologic actions and interactions with other drugs, routes of administration, vehicle, toxic signs, lethal dose, time of death, etc.

3. Multidose toxicity studies (subchronic, carcinogenicity, pharmacologic, and interactions with other drugs). Provide a table of studies including species and strain, number of animals, sex, age, dose, dose schedule, and route of administration. Notable treatment and dose-related changes in survival, per-

cent weight gain, toxic signs, hematology, clinical chemistries, organ weight, and pathology should be provided.

4. *Carcinogenicity* studies. The following information should be included:

   (a) For each treatment group, the number of animals entered and surviving 12, 15, 18, 21, and 24 months.
   (b) A summary table of tumor occurrences with deaths and sacrifices combined, organized by body system, tumor type, and dose level.
   (c) In the above table, each tumor shown to have a statistically significant dose response (positive or negative) at the $P = 0.05$ level (one-sided) using a mortality-adjusted statistical test of dose response over the entire study time unadjusted for multiple comparisons or multiple testing should be indicated. Calculated P values for the significant dose-response test for each of these tumors should be included.

5. Special toxicity studies.
6. Reproduction studies.
7. Mutagenicity studies.
8. ADME (absorption, distribution, metabolism, excretion) studies

Animal species should be presented under each group by smallest (mouse) up to largest (monkey or other mammals). The route of administration should be presented under each species tested and the treatment group under each route of administration. For special toxicity studies, such as irritation and hemolysis studies, tabulate data as appropriate. An example of the format would be:

Acute toxicity studies
A. Mouse
   (1) Oral
      (a) Untreated control
      (b) Vehicle control
      (c) Etc.
   (2) I.V.
      (a) Untreated control
      (b) Vehicle control
      (c) Etc.
B. Rat
   (1) Oral
      (a) Untreated control
      (b) Vehicle control
      (c) Etc.
   (2) I.V.
      (a) Untreated control
      (b) Vehicle control
      (c) Etc.

For *reproduction* studies, tabulate fertility and reproductive performance studies (segment I) and perinatal and postnatal studies (segment III) if differences are observed from controls. Teratology study data (segment II) should be tabulated showing differences and similarities in gross viscera and skeletal anomalies.

For *mutagenicity* studies, data should be presented in the following order:

1. In vitro nonmammalian cell system
2. In vitro mammalian cell system
3. In vivo nonmammalian system
4. In vivo mammalian system

In summarizing the ADME studies, tabulate species, strain, and dose comparison data by the following:

Peak level, half-life, and so forth
Plasma protein binding
Tissue distribution/accumulation
Enzyme induction or inhibition
Metabolites
Excretion pattern and characteristics

The absorption, distribution, metabolism, and excretion in the species used in the toxicology studies should be discussed. Quantitative or notable qualitative differences in ADME between the various animal species and humans should be discussed, as well as any references to observed species differences in toxicity and extrapolation of the findings to humans. The significance of these findings to the interpretation of the results of the carcinogenicity, bioassay, and other preclinical toxicity studies should be considered.

F. Human Pharmacokinetics and Bioavailability Summary

The human pharmacokinetic and bioavailability summary should include the following:

1. A brief description of each bioavailability study of the drug in humans, by type, objective, design, analytical and statistical method used, and results.

2. A brief description of the pharmacokinetic characteristics of the active ingredient(s) and the performance of the dosage form, integrating conclusions from the bioavailability and pharmacokinetic studies and from clinical studies performed. Information on volume of distribution, half-life, routes and rates of excretion, and metabolism of each dosage form studies, and the proportionality of absorption over the therapeutic dose range should be included. If pertinent, a comparison with the bioavailability of other dosage forms should be provided.

Any identified differences in pharmacokinetics among patient subgroups should be cited (age, renal status, etc.).

3. A description of the dissolution profile of the drug.

G. Microbiology Summary

For anti-infective and antiviral drugs, provide a summary of the results of the microbiologic studies conducted with the drug. This should include the following:

- A brief description of the known mechanisms of action together with structural or other similarities to known families of antimicrobial drugs.
- A brief description of the antimicrobial spectrum of action and a summary of the results of in vitro susceptibility testing demonstrating the concentrations of the drug required for effective use.
- A brief description of known mechanisms of resistance to the drug and results of any in vitro studies regarding resistance or any known epidemiologic studies that demonstrate prevalence of resistance factors.
- A brief description of the clinical microbiology laboratory test method needed for effective use of the drug.

H. Clinical Data Summary and Results of Statistical Analysis

The clinical data summary and results of statistical analyses are divided into several parts as presented below. This section is probably the most scrutinized by the FDA's clinical reviewer. It is the basis of efficacy and safety that will determine an NDA approval.

1. Clinical Pharmacology

Describe the phase 1 studies that establish human tolerance to the drug, absorption, distribution, and elimination kinetics, blood concentrations as a function of time after dosing, the metabolic profile, drug interactions, dependence, and pharmacologic effects at various doses. Although it is usual to test the drug during phase 1 studies in normal (healthy) subjects, if a drug has dramatic biochemical or pharmacologic effects tailored to address a specific disease state, phase 1 studies are conducted only in individuals with such a disease state. A careful explanation in this section should be prepared. Information may be formatted as follows:

- A tabular presentation of studies by protocol, investigator, study design (e.g., randomized, double-blind, open, parallel, crossover), drug or other treatment used for comparison (if any), number of subjects (or patients, if used), age, sex, dose, and duration of dosing. Location of study report and CRFs (if submitted) should also be included.

- A short narrative description of the design and results of each study.
- Conclusions drawn from this group of studies. A summary should provide the critical findings, especially those relevant to clinical use of the drug (e.g., dose-response or blood level-response data, duration of action, and any specific potential problems associated with metabolism or excretion). There should be a complete discussion of data pertinent to other common important pharmacologic properties, including cardiac electrophysiologic effects, hemodynamic effects, anticholinergic effects, and effects on the central nervous system. Any effects related to age or sex should be highlighted.

2. *Overview of Clinical Studies*

The objective of all clinical studies is to produce clear and well-documented evidence that a new drug candidate is effective and safe when used in the manner intended. The clinical experience that the sponsor is submitting (see GCP chapter 13) must provide assurance of the care taken in the evaluation of the drug product. This assurance must be passed on to the FDA reviewer in the summary of the clinical evaluation.

The overview should reference any specific FDA guidelines used and any FDA-sponsor discussions held on major issues, such as an end-of-phase 2 conference. The critical features of the trials should be explained, including duration, study design, and particular advantages or potential problems examined. If there is pertinent clinical literature (controlled or uncontrolled clinical studies or reports on patients), a review may be helpful. (The sponsor may want to comment on literature pertaining to closely related drugs that provide insight into potential problems or areas of special interest.)

It is important to comment on all studies of the drug, even those not completed or ongoing, or studies of claims other than those for which approval is sought.

3. *Controlled Clinical Studies*

All controlled studies, whether they provide positive, equivocal, or negative evidence, should be included. The recommended sequence for presentation, for each indication, is as follows:

- A table of all completed studies sponsored by the applicant, including domestic studies and foreign studies, as well as those from published or unpublished papers or other sources. Provide the protocol number (where available), reference to any published report, investigator(s), study design (e.g., double-blind, open, parallel, crossover), the formulation and dosage used, number of patients, demographics of patients, dose and duration of therapy, and location of the clinical report and CRFs.

- A short narrative of each study, including study design, conduct, and analysis. This section should be of sufficient detail to allow the reader to understand what the dose was and what data were collected and analyzed for efficacy and safety determinations. Quantitative results should be provided, and the statistical methodologies, specific endpoints used, and any patient inclusion and exclusions should be described.
- An analysis of each study and all the studies as a whole to demonstrate how they relate to each claim of effectiveness. If some studies are considered more important than others, this should be noted and an explanation given. Any pooled analyses should be explained and presented. Any major inconsistencies or areas needing further exploration should be identified. Dose-response and dose-duration/dose-frequency information as well as any differences in response among subgroups should be included.

4. *Uncontrolled Clinical Studies*

This section should include the following:

- A table of studies similar to that included in the controlled clinical studies section of the summary. The information should include the protocol number or other identifier, conditions studied, formulation and dosage, number of patients, age and sex, duration of therapy, and location of the full report in the clinical data section.
- A brief narrative description of the design and results of each study, including effectiveness results and adverse experiences.
- An overall analyses of these studies and the conclusions reached from them.

5. *Other Studies and Information*

A brief description of any studies not included in the clinical pharmacology, controlled clinical studies, or uncontrolled clinical studies sections should be included here. These may include studies and publications not directly related to the claims sought in the application but that provide pertinent safety information. Analyses of marketing experience or epidemiologic data may also be included in this section.

6. *Safety Summary—General Safety Conclusions*

This section will include the following information:

a. Extent of Exposure

The extent of drug exposure and the number of patients exposed to the drug for various periods and at various doses. These should include all subjects or patients.

b. Adverse Events

Data from controlled and uncontrolled studies should be integrated to provide estimated rates of adverse events. The tables of adverse event rates, including the more serious or frequent events, should be compiled (see Chapter 9 on ADR reporting). It is useful to analyze results from controlled and open studies separately and distinguish short-term use from longer-term studies. Any differences in rates related to dose, duration of therapy, and patient characteristics should be identified. Data related to drug-drug interactions should also be included. An analysis of patients who left the study prematurely because of an adverse event or who died while on this study drug should be included. For potentially serious adverse events that have not been established as drug related, the data should be discussed along with additional steps in premarketing or postmarketing, to determine whether the drug is associated with this effect.

c. Clinical Laboratory Data

Provide a short summary of these data, noting clinically significant trends and statistically significant changes. The summary should compare the active control drug with placebo and should show the numbers of patients receiving each test. Also identify and evaluate those patients who leave a trial because of clinical laboratory abnormalities.

d. Summary of Other Safety Assessments

If there were any special safety examinations performed (e.g., audiometric, electrocardiographic, or ophthalmologic examinations), these should be summarized here. Include any comparisons with active control drugs and placebo, if available, and the numbers of patients receiving each test.

e. Overdosage

Any information available on the treatment of overdosage should be included.

f. Drug Abuse

If the drug is subject to abuse, provide a summary of the studies or other relevant information. If the drug is not considered abusable but is a member of a class of drugs known to have abuse potential, and if studies of its abuse potential have not been performed, then the reasons these studies were considered unnecessary should be discussed.

I. Discussion of Benefit/Risk Relationship and Proposed Postmarketing Studies

On the basis of the results of effectiveness trials and the toxicity of the drug in human and animal studies, a benefit-to-risk assessment of the drug should be formulated and presented. The assessment should consider the risks and benefits of alternative treatment(s) for the target population identified in the labeling.

The applicant should also describe any proposed postmarketing clinical studies and the reasons for doing such studies, e.g., to study further a suspected adverse reaction, or studies in children if there is a potential for use in this group.

V. NDA TECHNICAL SECTIONS

The guidelines for the format and content of each relevant technical section should be reviewed for specific information. Included below are brief, general descriptions and outlines of the NDA technical sections.

A. Chemistry, Manufacturing, and Controls

This section of the NDA, called the CMC section, requires extreme attention and precision in its presentation. Therefore, these requirements and applicable guidelines for the chemistry, manufacturing, and controls section of an NDA submission are discussed in detail in Chapter 7 of this book.

B. Nonclinical Pharmacology and Toxicology

In this section, it is useful to include a summary of the preclinical studies as well as complete reports. A table of contents with the volume and page numbers for the location of each report should also be included. New studies or final reports not previously submitted to the IND or to a previous NDA submission for the drug under review should be identified in a consistent and conspicuous manner in the table of contents.

The FDA guidelines specifying the order in which the nonclinical pharmacology and toxicology studies should be presented in an NDA submission, as follows:

1. Pharmacology studies
2. Acute toxicity studies
3. Multidose toxicity studies
4. Special toxicity studies
5. Reproduction studies
6. Mutagenicity studies
7. Absorption, distribution, metabolism, excretion (ADME) studies

When more than one species is used, the following order of presentation is recommended, with males preceding females:

1. Mouse
2. Rat
3. Hamster
4. Other rodent(s)
5. Rabbit
6. Dog
7. Monkey
8. Other nonrodent mammal(s)
9. Nonmammals

Data for typical adult animals should precede that of infant, geriatric, or disease-model animals. Age and weight ranges, strains, and animal suppliers should be specified in each study.

Regarding route of administration, the one that represents the intended route in humans should be presented first, followed by data from other routes in the following relative order:

1. Oral
2. Intravenous
3. Intramuscular
4. Intraperitoneal
5. Subcutaneous
6. Inhalation
7. Topical
8. Other in vivo
9. In vitro

Multiple-dose data should be displayed from lowest to highest dose as shown below:

1. Untreated control
2. Vehicle control
3. Low dose
4. Middle dose(s)
5. High dose
6. Positive or comparative control(s)

Dose should be based on the active moiety component and should be expressed on a body-weight basis if possible. When the drug is administered in diet or drinking water, the daily dose, calculated periodically from actual body weight and food or water consumption data, should be included in the report as the dose range per sex for each group at the beginning and end of the study and at designated intervals throughout a chronic study. Doses should not be expressed solely as a concentration in food or drinking water. One should also obtain blood level data to confirm that the drug is being absorbed by the animals.

C. Pharmacology Studies

Pharmacology studies related to the therapeutic indication should be presented first, followed by those related to possible adverse reactions and interactions with other drugs. Within the three categories listed above, the data should be grouped in the following order:

1. Gastrointestinal
2. Genitourinary
3. Endocrine
4. Anti-inflammatory
5. Immunoactive
6. Chemotherapeutic
7. Enzyme effects
8. Other

Where possible, data should be summarized in tabular form, with the various studies within each category grouped to present a coherent pharmacological profile of the drug.

D. Acute Toxicity Studies

The pretest conditioning and age of the animals, dosing procedures, vehicle used, and dosage volumes should be specified. The description of the results should include the types and severity of toxic signs and their onset and progression or reversal in relationship to dosage and time after dosing. The lethal dose data should be tabulated, including the total number dosed and mortality incidence with time of death for each sex at each dose.

E. Subchronic/Chronic/Carcinogenicity Studies

At the beginning of this subsection, all studies should be listed and briefly described in a table. Studies should be grouped by species, order of increasing duration of treatment, and route of administration. The table should include animals species and strain, initial group size per sex, dosing route and mode of drug administration, dose groups, duration of the study in weeks, week of any scheduled interim sacrifices, the name of the laboratory performing the study, and the report number.

Within each individual study report, there should be a description of the protocol, followed by study results.

In the section of the report that describes how the study was conducted, the following information should be included:

Species, strain, source, age
Sex, number at beginning and end of the study
Route and mode of administration
Calculated dosage levels and ranges
Rationale for dose selection
Administration of vehicle or control treatment
Drug batch or lot number
Duration of treatment
Duration of study
Interim sacrifice

The results of the study should include the following:

Observed effects
Mortality
Body weight
Food/water consumption
Physical examination
Hematology/bone marrow/coagulation
Blood chemistry/urinalysis/ADME data
Organ weights
Gross pathology
Histopathology

For *carcinogenicity* studies, tumor data for male and female animals should be presented separately. A chronologic listing should be prepared showing the period in which each tumor was discovered, the dose group of the animal, the animal number, whether the animal was sacrificed or died, the site of the tumor, the tumor type, and an assessment of the malignancy of the tumor.

A summary table should be prepared for each period in which a death or sacrifice occurred, and for each dose group the number dying, the number sacrificed, the number of animals necropsied completely, and the number necropsied to any extent. This section should also include a summary table of tumor occurrences with deaths and sacrifices combined, organized by body system, organ, tumor type, and dose level. The number of animals with tumors of the stated type should also be included.

For each tumor found to be statistically significant at the $P = 0.05$ level (one sided) by use of a statistical test of dose response over the entire study that is adjusted for mortality as appropriate and that is not adjusted for multiple comparisons or multiple testing, the following information should be included:

1. The estimated incidence rate of fatal tumors in each time period and the prevalence rate of nonfatal tumors in each time period.
2. The statistical test used and the calculated P-value should be included.

Results for both statistically significant positive and statistically negative dose-response findings should be reported.

F. Special Toxicity Studies

This section includes studies appropriate to a particular formulation or route of administration, such as in vitro hemolysis or irritation at the injection site. In vivo results should be tabulated to show group comparison and time-related or progressive effects within each group. For in vitro studies, the data should be tabulated by type of test or test system, dose range, and effects related to dose.

G. Reproduction Studies

This section should include a summary table similar to that included in the subchronic/chronic/carcinogenicity studies section.

Segment I studies of fertility and reproductive performance should be presented first, followed by segment II teratology, and segment III perinatal and postnatal; any other studies such as multigeneration studies should be presented last. Observations and their incidence in relationship to dosage or time should be presented in the following relative order:

- Maternal effects and day of parturition/necropsy (and paternal effects in segment I)
- Maternal necropsy
  - Corpora lutea
  - Uterine contents
  - Implantation
  - Dead fetuses
- Fetuses (grouped by litter)
  - Sex ratio
  - Weight
  - Viability
  - Gross observations
  - Visceral abnormalities
  - Skeletal abnormalities
- Neonates to weaning
  - Sex ratio
  - Viability
  - Growth
  - Behavior and performance
  - Anatomical abnormalities

H. Mutagenicity Studies

The results of these studies should be tabulated by type of study methods used, dose range, and effect at each dose. Studies should be presented in the following order:

1. In vitro nonmammalian cell system
2. In vitro mammalian cell system
3. In vivo mammalian system
4. In vivo nonmammalian system

I. ADME Studies

These studies should be summarized in the following sequence:

1. Absorption, pharmacokinetics, serum half-life, etc.
2. Protein binding
3. Tissue distribution/accumulation
4. Enzyme induction or inhibition
5. Metabolism characteristics and metabolites
6. Excretion pattern

If possible, ADME data should be generated on the same species used in the toxicology studies.

J. Human Pharmacokinetics and Bioavailability Section

Included in the first portion of this section should be an overall tabulated summary of all in vivo biopharmaceutical studies carried out on the drug grouped by type of study. The study number, route of administration, dosage form, batch number, plant and date of manufacture, number of subjects, IND or NDA number under which the study was conducted or study submitted, date of submission, conclusions regarding the study, and previous agency response on the study or the protocol together with the date of the correspondence should be included.

The next section is a summary of the bioavailability/pharmacokinetic data and the overall conclusions. The summary should include a table with the following pharmacokinetic parameters: peak concentration (Cmax), AUC, time to reach peak concentration (Tmax), elimination constant (kel), distribution volume (Vd), plasma and renal clearance, and urinary excretion. Overall conclusions as well as any unresolved problems should be discussed.

In the third section, a list of all formulations used in clinical trials and in vivo bioavailability/pharmacokinetic studies together with the studies in which each formulation was used should be provided. For batches used in bioavailability/pharmacokinetic studies, significant manufacturing and formulation changes for the drug product over the course of its evaluation should be identified.

The fourth section relates to the analytical methods used to measure the levels of the drug and major metabolites in body fluids. A table should be included in this section listing the study number, submission date, type of biological fluid, method used, sensitivity, and range of the method and specificity of the method for the parent compound and metabolites.

Dissolution data on each strength and dosage form for which approval is being sought should be provided in the fifth portion of this technical section. A comparative dissolution study with the lot(s) used for in vivo biopharmaceutic studies should also be included.

The date of the studies, dosage form and strength, lot number, dissolution apparatus, media/temperature, speed of rotation/flow, collection times, the number of units tested, range and mean percent dissolved, should all be included in the table. A summary of the dissolution method and specification for the product should be provided.

The last portion of this technical section includes the reports for each of the studies referenced in this section. Each report should include the following information:

Objective
Dosage form studied
Investigator
Clinical facilities
Analytical facilities
Individual subject/patient data including demographics, concomitant medication, blood/urine levels, laboratory tests, and adverse reactions
Documentation on the sensitivity, linearity, specificity, and reproducibility of the analytical methods.

The data analyses should include appropriate statistical analysis usually involving analysis of variance, calculations of power analysis, 95% confidence intervals, and ratio analysis. The details of pharmacokinetic parameter calculations, including pharmacokinetic models and equations used, should be adequately described and referenced. A brief summary of study conclusions should be provided.

K. Microbiology

New drug applications for anti-infective and antiviral drugs require a technical section on microbiological data. This section should include the biochemical basis of the drug's action on microbial or viral physiology, the antimicrobial or antiviral spectrum of the drug including results of in vitro preclinical studies demonstrating concentrations of the drug required for effective use. Any known mechanisms of resistance to the drug including the results of any known epidemiologic studies demonstrating prevalence of resistance factors and clinical microbiology laboratory methods to evaluate the effective use of the drug also should be included. This section is divided into the following 11 sections.

1. Mechanism of Action

The mode of action of the drug, together with its chemical structure and any structural or other similarities to known antimicrobial drugs should be included.

2. Pharmacokinetics

In this section, the pharmacokinetics for systemic dosage forms should be described, including absorption, routes of excretion, protein binding, metabolic changes to compounds of lesser or greater activity, and distribution into various pharmacokinetic compartments. References to the locations in the NDA of the full reports of the pharmacokinetics studies should be provided.

3. Antimicrobial Activity

A description of the antimicrobial spectrum of the drug and a summary table of the major in vitro susceptibility studies should be included.

4. Enzyme Hydrolysis Rates

The stability of the drug in the presence of enzymes produced by microorganisms should be summarized.

5. Miscellaneous Studies

If applicable, any miscellaneous studies, such as those showing bacterial effects, activity of major metabolites, or relationships to known drugs, should be summarized.

6. Assessment of Resistance

A brief summary of the resistance to the drug should be included. A detailed discussion of the studies of resistant microorganisms as well as any resistance known to occur among normally susceptible species is also required. It is suggested that a table be prepared including each species or type of microorganism tested, antimicrobial drugs to which each microorganism is resistant, number of microorganisms tested, and percentage of microorganisms susceptible to the drug at each level of resistance.

7. *Clinical Laboratory Susceptibility Test Methods*

A detailed discussion of the development of clinical laboratory susceptibility test methods should be provided.

8. *In Vivo Animal Protection Studies*

The results of any efficacy studies in experimentally infected animals should be summarized.

9. *In Vitro Studies Conducted During the Clinical Trials*

The susceptibility testing of clinical isolates obtained in the clinical investigations should be summarized.

10. *Conclusions*

A brief narrative summary of the overall results and any conclusions about the drug must be included in this section.

11. *Published Literature*

Included in this section is a bibliography and copies of all published reports of studies used in support of the data and information contained in the microbiology section.

L. Clinical Data Section

The clinical data section is probably the most important and most complicated section of an NDA. It is the part that provides the safety and efficacy data on the drug for its intended use. In the *Guidelines for the Format and Content of the Clinical and Statistical Sections of an Application*, FDA has outlined how it would like to see this section of the NDA organized. This outline is provided below.

M. Outline of the Clinical Section

A. List of investigators, list of INDs and NDAs
B. Background/overview of clinical investigations
C. Clinical pharmacology
    1. Table of all studies, grouped by study type
    2. ADME studies
        a. Synopsis of each study
        b. Full report of each study
        c. Summary and evaluation of all studies

3. Early dose-tolerance studies
   a, b, c, as above
4. Short-term studies of therapeutic response or of a pharmacodynamic effect thought to relate to therapeutic response, including dose-response and blood level-response studies
   a, b, c, as above
5. Studies of pharmacodynamic properties other than the property thought to be related to clinical effectiveness
   a, b, c, as above
6. "Special" studies
   a, b, c, as above
7. Overall summary of clinical pharmacology

D. Controlled clinical studies
   1. Table of studies, grouped by indication, study design, completion status, location, and availability of case reports. If more than one indication is included in the NDA, each section should be divided by indication.
   2. Indication 1
      a. Placebo-controlled studies
         1) Completed studies
            a) Domestic, full case reports available
               (1) For each study, information should be provided as follows:
                  i. Brief synopsis
                  ii. Protocol
                  iii. Related publication
                  iv. List of investigators
                  v. Integrated clinical and statistical report
            b) Foreign, full case reports available
               (1) Data for each study should be provided as in i–v above
            c) Published reports and other reports lacking full case reports
               (1) Again, data for each study should be provided (as appropriate) as in i–v above
         2) Ongoing studies with interim results
            (a–c) as above
         3) Incomplete studies no longer active
            (a–c) as above
      b. Dose comparison concurrent control studies
         (1–3) as above
      c. No-treatment concurrent control studies

        (1–3) as above
      d. Active treatment concurrent control studies
        (1–3) as above
      e. Explicit historical control studies
        (1–3) as above
   3. Any additional indications should be organized as in Indication 1, above
   4. Optional overall summary and evaluation of data from controlled trials

E. Uncontrolled clinical studies
   1. Table of all studies, grouped by indication, completion status, location, and availability of case reports
   2. Indication 1
      a. Completed studies
         1) Domestic, full case reports available
            a) For each study, information should be provided as listed below:
               (1) Brief synopsis
               (2) Protocol
               (3) Related publication
               (4) List of investigators
               (5) Report of the study
         2) Foreign, full case reports available
            a) As above
         3) Published reports and other reports lacking full case reports
            a) Complete studies as above
            b) Incomplete studies
               (1–3) as above
   3. Any additional indications should be organized as in Indication 1, above

F. Other studies and information
   1. Table of all studies
   2. Controlled studies of uses other than those claimed in the application, any study design, complete or incomplete
      a. Studies with case reports available
         1) For each study, information should be provided as outlined below
            a) Brief synopsis
            b) Protocol
            c) Related publication
            d) List of investigators
            e) Report of the study

        - b. Studies without case reports available
            - 1) As above
    - 3. Uncontrolled studies of uses other than those claimed in the application
        - a. Studies with case reports available
            - 1) For each study, information should be provided as outlined below
                - a) Brief synopsis
                - b) Protocol
                - c) Related publication
                - d) List of investigators
                - e) Report of the study
        - b. Studies without case reports available
            - 1) As above
    - 4. Commercial marketing experience
        - a. List of countries in which drug has been approved
        - b. Reports from regulatory authorities
        - c. Epidemiologic studies
        - d. Spontaneous reports from foreign marketing experience of serious adverse experiences
    - 5. Reports from literature or elsewhere not otherwise reported
        - a. Published case reports, letters, etc.
        - b. Other information
- G. Integrated summary of effectiveness data
    - 1. Identification of studies fulfilling the statutory requirements for adequate and well-controlled studies showing that the drug has its intended effect
    - 2. Comparison and analysis of all controlled trials
    - 3. Results of uncontrolled studies
    - 4. Analysis of dose-response or blood-level response information
    - 5. Analysis of response in subsets of the overall population: drug-demographic, drug-drug, and drug-disease interactions
    - 6. Evidence of long-term effectiveness, tolerance, and withdrawal effects
- H. Integrated summary of safety data
    - 1. Table of all investigations pertinent to safety, identified by protocol number and principal investigator, grouped by study type
    - 2. Overall extent of exposure
    - 3. Demographic and other characteristics of the study population
    - 4. Adverse experiences in clinical trials
        - a. Narrative summary of adverse events
        - b. Display of adverse events and occurrence rates

    c. Analysis of adverse event rates
    d. Display and analysis of deaths, dropouts due to adverse events, and other serious or potentially serious adverse events
  5. Clinical laboratory evaluation
  6. Adverse events, including laboratory abnormalities, from sources other than clinical trials
  7. Animal data
  8. Analysis of dose-response information
  9. Drug-drug interactions
  10. Drug-demographic and drug-disease interactions
  11. Pharmacologic properties other than the property of principal interest
  12. Long-term adverse effects
  13. Withdrawal effects

I. Drug abuse and overdosage
J. Integrated summary of benefits and risks of the drug

Some parts of the clinical data section are discussed in greater detail below.

1. List of Investigators; List of INDs and NDAs

This section should contain a complete alphabetical list of all the names and addresses of all known investigators that the applicant supplied with the drug substance or product. In addition, all dosage forms used by these investigators should be stated. This list should also include the kinds of studies carried out, study identifier, location of each report, case report tabulations, and case report forms. In addition, a list of all known INDs under which the drug was studied and any other NDAs submitted for the same drug substance should be included.

2. Background/Overview of Clinical Investigations

This is a very important part of the clinical data section of an NDA. It provides the medical reviewer with a summary of how the drug was developed. Because of the time required for the clinical development of a product, many times the FDA reviewers assigned to the project have changed. As a result, the NDA may be reviewed by a new set of individuals who are unfamiliar with the history of the development of the project. It is also possible that the standards for research in the particular field may have changed and what was standard clinical practice when the clinical studies were initiated is no longer the method of choice for studying the particular class of drugs. In this section, one is given the opportunity to describe the general approach and rationale used in developing the clinical data. This discussion should include how information derived from clinical pharmacology studies led to critical features of the clinical studies. The basis for the critical design features of the clinical trials as well as their suitability and selection of major clinical endpoints also should be discussed. Any FDA drug-class or other guidelines used in designing the studies and the rationale for any deviations from the guidelines should be discussed.

Food and Drug Administration/Sponsor discussions concerning issues related to the clinical program, the major agreements reached, and any important differences between these agreements and the ultimate conduct of the clinical studies must be referenced. The selection of areas of special interest for study and analysis, and effectiveness or safety issues raised by drugs of the same pharmacologic or therapeutic class warrant discussion. Any specific questions raised by the results of the clinical trials or by experience with related drugs and not answered by the clinical studies should be cited, together with an explanation as to how the sponsor plans to handle these issues. Any planned studies in support of an additional indication also should be noted here.

3. *Clinical Pharmacology*

As noted in the outline of the clinical data section of an NDA, this section is divided into five parts. It should also include a table of all studies grouped by type and an overall summary of the clinical pharmacology studies. The table should list investigators, study identifiers, starting date of the study, and location of the study report, tabulations, and case report forms. Other information, including number of subjects, study design, formulation and dosage strength used, control treatment, dose range, dose regimen, and duration of dosing should also be included. For each group of studies, there should be a 1- to 2-page synopsis of the results of each study, followed by the complete report of the study. At the end of each of the five sections, there should be an overall summary and evaluation, including a narrative or tabular comparison of the human studies with the animal pharmacology and toxicology data.

An overall summary of the clinical pharmacology data should be included. In this summary, findings relevant to clinical use of the drug, such as dose-response or blood level response data, duration of action data, and potential problems that can be associated with the observed patterns of metabolism or excretion must be discussed.

4. *Controlled Clinical Studies*

Before a detailed discussion of the information to be included in this section is given, it is useful to review the definition of adequate and well-controlled studies. Approval of a new drug requires substantial evidence of effectiveness. Substantial evidence is defined under the Federal Food, Drug and Cosmetic Act as

> "evidence consisting of adequate and well-controlled investigations by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and

> responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling. The requirement for well-controlled investigations has been interpreted to mean that the effectiveness of a drug should be supported by more than one well-controlled trial and carried out by independent investigators."

Recently, there has been active labeling to accept a single pivotal clinical trial as the basis for approval. This thrust is based on the FDA Modernization Act (FDAMA) of 1997. Section 115 of FDAMA states that the "substantial evidence" of efficacy requirement may be satisfied by *one* adequate and well-controlled clinical investigation supported by confirmatory evidence. The FDA issued a guidance on when one phase 3 trial would suffice in May 1997.

In this section of the NDA, all controlled studies including those that were incomplete and abandoned must be provided. For studies intended to support effectiveness, full reports are required; for others, an abbreviated report may be acceptable.

A table of all studies grouped by indication and type of control, as shown in the outline, should be included. The table lists investigators, study identifiers, starting date of the study, location of the report, tabulations, and case report forms. The number, age, and sex of the subjects, study design, formulation, dosage form and strength, control, doses, and duration of dosing also should be provided. The order of presentation of the studies should be as indicated in the outline. Completed studies should be presented before ongoing studies with interim results, followed by incomplete studies.

Reports of individual studies should include a 1- to 2-page synopsis, a copy of the protocol, any publications on the data, a list of all investigators and other persons whose participation materially affected the conduct of the study, and a brief description of their training and role in the study. A statement regarding compliance with the IRB regulations in 21 CFR Part 56 and the informed consent regulations 21 CFR Part 50 is also required.

In a presentation, Dr. Robert Temple, Director of the Office of Drug Research and Review at FDA (1), suggested the following approach to the presentation of individual studies in the clinical data section:

Synopsis: prepare a brief (1-page) summary of the study.
Manuscript: provide a short summary (about 10 pages) for major studies.
Comprehensive summary: for all studies, present a detailed description of the study design and results, including the following:

- Investigator
- Study objectives
- Detailed design
- Patient selection criteria

- Clinical observations and laboratory measurements
- Evaluation criteria
- Planned statistical analyses
- Method of eliciting adverse experiences
- Comparability of treatment groups for demographic and other variables
- Analysis of effectiveness results
- Detailed accounting of patients entered/excluded from the study
- The dosage and duration of treatment

This critical section should include individual patient data in a tabulated form. Demographic values (age, sex, race, etc.), patient inclusion and exclusion criteria, relevant clinical measures for the particular study must also be included. Special clinical and laboratory measures used for the study must have a rationale for these tests as well as an explanation for the significance of the results. All concomitant medications used during the clinical trial must be listed for each patient admitted into the study. Other clinical observations of less relevance should be addressed.

Safety information should be presented as a summary of adverse experiences by frequency and body system, except for patients who died or who left the study prematurely because of an adverse event. These should be described in detail, and the role of the drug should be evaluated for each reaction. The safety analysis should consider abnormal laboratory values as well as adverse experiences, and the following points should be kept in mind:

1. Is the patient receiving several different medications simultaneously?
2. Are the patient's complaints totally subjective, e.g., headache, nausea, dizziness? Many of these often appear in healthy volunteers taking placebo.
3. The evaluation of adverse experiences is dependent in great part on the extent of the control of the study.
4. The effect of the environment in which the study was conducted—acute medical ward vs. outpatient sample.
5. Examination of patient's history and careful follow-up of patient; authentication of facts.

An applicant may provide an overall summary of data from controlled studies. This section is optional and many firms do not include it because the results of the studies are presented in the integrated summaries of efficacy and safety, which will be discussed later in this chapter. The *Guidelines for the Clinical and Statistical Sections of a New Drug Application* also address the format and content of an integrated clinical/statistical report for a clinical study; this too will be discussed later.

5. *Uncontrolled Clinical Studies*

Uncontrolled studies will not, in general, be useful in contributing to substantial evidence of effectiveness of a drug, but they can provide support for controlled clinical studies and provide safety information. The format for this section is the same as that contained in the outline. As in the controlled clinical studies section, this section should begin with a table, followed by the reports for the studies. Data should be provided in the same manner as that discussed in the controlled clinical studies section.

6. *Other Studies and Information*

In this section, a description and analysis of any additional information obtained by the applicant from any source, foreign or domestic, that is relevant to the evaluation of the efficacy and safety of the product should be included. It may include results of controlled or uncontrolled clinical trials of uses of the drug other than those claimed in the application, commercial marketing experience, and reports in the literature or otherwise obtained, other than those cited in the controlled trials and uncontrolled trials sections of the clinical data section.

This first part of this section is a table of all the studies listing the same information contained in the tables in the controlled clinical trials and uncontrolled clinical trials sections of the clinical data section. Reports of the studies should be presented as shown in the outline. The content of the reports for the studies should be the same as those discussed in the other sections.

The next portion of this section deals with commercial marketing experience and foreign regulatory actions. This part should contain the following information:

1. A list of the countries in which the drug has been approved with dates of approval and a list of the countries in which approval has been applied for with the dates of the applications.
2. All reports from foreign regulatory authorities or foreign affiliates, licensors, or licensees of the applicant, including reports and analyses of adverse effects, warning letters sent to physicians, and major changes in marketing status or labeling information resulting from marketing or other experience.

A copy of any letter from a foreign regulatory body that refuses drug approval on safety grounds should also be included. It is requested that copies of approved labeling from European countries, Canada, Australia, New Zealand, and Japan be included together with English translations. Important differences between these and the proposed United States labeling with respect to contraindications, warnings, precautions, adverse reactions, or dosing instructions should be identified and explained.

3. Epidemiologic studies.

4. Spontaneous reports from foreign marketing experiences of serious adverse experiences.

Reports from the literature that are not included in other sections of the NDA should be provided in this section.

7. Integrated Summary of Efficacy

This section should provide an integrated summary of the data demonstrating substantial evidence of effectiveness for each claimed indication. It should also include a summary of the evidence supporting the dosage and administration section of the labeling, including the dose and dose interval recommended.

In this section, an overview of the results should show that the regulatory requirements for approval have been met by adequate and well-controlled studies that support the claimed effect. This is especially important if results are inconsistent or marginal. An examination of study-to-study differences in results, effects in subsets of the treated population, dose-response information, and comparisons with alternative drugs should be addressed. A description of the information to be included in this section is contained in the outline provided earlier in this chapter.

The first portion of this section is an identification of those studies that fulfill the requirements for adequate and well-controlled studies showing that the drug has its intended effect. This is followed by a discussion of those studies as well as the data from all controlled clinical studies. Any differences in outcome between studies of similar design should be explained where possible. Tables showing major study design features, numbers of patients, numbers of dropouts, and major outcomes are sometimes useful.

The results of uncontrolled studies should be discussed to the extent that they provide supportive evidence of effectiveness. This is followed by an analysis of dose-response or blood level-response information. This section should include: (a) an integrated summary and analysis of all data, from animal, pharmacokinetic, pharmacodynamic, and other clinical pharmacology studies, and from controlled and uncontrolled clinical studies that bear a dose-response or blood level-response relationship to effectiveness, (b) the method of dose selection, and (c) the choice of dose interval. Data that support the dosing recommendation proposed in labeling, including the recommended starting and maximal doses, the method of dose titration, and other methods regarding individualization of dosage also should be discussed. Any deviations from relatively simple dose-response or blood level-response relationships due to nonlinearity of pharmacokinetics, delayed effects, tolerance, etc., as well as limitations of the data, should be described.

If dosing recommendations are different from those in other countries, the differences should be explained along with the reasons for using different dosages and different delivery systems, if applicable.

Differences in dose-response relationship in age, sex, disease, or other subpopulations should be described. The gnawing concern that FDA drug developers and the scientific community have about drug response in different populations need to be addressed in this section. Any data regarding subsets of the population receiving the drug should be clearly presented. Adequate information about the effects of the drug in women should be clarified in an analysis capable of identifying potential gender differences in drug efficacy and safety. Considerations should entail differences of age, ethnic background, metabolic phenotype, body fat content and distribution, and body size.

An analysis of responses in subsets of the overall population is required. The extent of this part of the integrated summary of efficacy will depend to a large extent on the drug and its intended patient population. Subsets of interest may include sex, race, age, disease severity, concomitant illness, concomitant drugs, smoking and alcoholism, and prior therapy.

8. Integrated Summary of Safety

This section integrates safety information from all sources, including pertinent animal data, clinical pharmacology studies, controlled and uncontrolled trials, foreign marketing experience (if any), and epidemiologic studies related to any use of the drug. Dose-response and blood level-response relationships for adverse effects should be identified, as should drug-drug or drug-disease interactions, and any demographic or clinical features that predispose to adverse effects. A description of any statistical analyses not included under the individual study reports should be provided. In this section, the safety analyses should examine all studies together, as well as possible safety concerns in different subsets of patients, which would be impossible in individual summaries because of the limited number of patients in each study. This also permits detection of more serious adverse experiences that were too rare to be seen in individual studies.

The format of the integrated summary of safety is provided in the following outline.

A table of all studies that provide safety information identified by protocol number, principal investigator, indication, and divided by type of study is required. This table should include the following information:

Type of study
Status (complete, continuing, discontinued)
Location of full clinical/statistical report
Availability of CRFs
Number of patients in each treatment group
Indications studied
Age range of patients in each study and sex/race distribution

Duration of drug exposure in the study
Dose range in the study
Frequency of dosing

The extent of exposure to the drug should be described in tables. This should include the number of patients exposed to the drug for specific periods, for example, 1 day or less, more than 1 day to 1 week, more than 1 week to 1 month, or more than 1 month. The numbers should be broken down by sex and other relevant demographic subgroups. Patients included in more than one study should be counted only once. If it cannot be determined whether the same patient appears in more than one study, this should be indicated.

The number of patients exposed to various doses for defined periods should be presented. Because many times this can be difficult to display, one possible way to approach this section is to attribute to each patient the dose he or she was given/or the longest time, providing a crude but reasonable picture of exposure. An alternative is to count each dose-duration segment for each patient exposed to several doses.

The relevant demographic, baseline, and other characteristics of the study population are addressed. These usually include the following:

Age
Sex
Race
Body weight
Primary diagnosis
Secondary diagnosis
Concomitant therapy taken during the study
Smoking status and history
Use of alcohol
Relevant prognostic variables

These should be presented for the entire drug-exposed population and for logical groups of studies, such as all controlled studies, short-term trials, long-term trials, etc. It is preferable that the same groupings be used in displaying adverse events.

The adverse event section of the integrated summary of safety is divided into four sections as provided in the following outline.

A. The first section is a narrative of the overall adverse event experience in all studies. The conclusions should be supported by the data and tabulations provided for the following three groupings.

1. A display of adverse events and occurrence rates. All new adverse events should be summarized in tables listing each event, the number of patients in whom the event occurred, and the occurrence rate. Although this information can be provided for all studies, excluding short-term studies (pooled together,

in many cases), it is better to perform separate analyses of those studies for which case report forms are available and those without case report forms. One may also consider grouping controlled studies, all trials excluding short-term studies in normal volunteers, or studies of similar duration together. Trials in which adverse events were reported by checklist or direct questioning versus those in which they were volunteered may also be handled separately. One may want to consider separating foreign and domestic trials. Which groupings are most appropriate will depend on the drug and the nature of the studies conducted.

2. Adverse events should be grouped by body system and arranged in decreasing frequency as well as divided into severity categories. They may also be further divided into those that are considered related and not related to study drug treatment. An explanation of how the relationship to the study drug was obtained should be included. Analysis of rates of adverse reactions is required. The most common adverse events that appear to be drug-related should be analyzed for relationship to dosage, dose interval, and duration of treatment, as well as to demographic characteristics. A final display of adverse reaction rates should be developed for use in labeling.

3. A display and analysis of deaths, dropouts due to adverse events, and other serious or potentially serious adverse events should be generated. The listing should include a patient identifier, study identification, location of the report, and location of the narrative description of the event. A table giving the rate of these events is also useful.

B. The second section should cover the following categories.

1. Clinical Laboratory Evaluation in Clinical Trials. In this section, data from individual studies should be combined and analyzed. Relationships between laboratory tests and clinically relevant subsets of patients as well as particular adverse events and laboratory abnormalities should be assessed. The relationship of drug-related abnormalities to dose, duration of treatment, and patient demographic characteristics should be explored where applicable.

2. Adverse Events, Including Laboratory Abnormalities, from Sources Other Than Clinical Studies. All sources of adverse events other than clinical trials, including foreign marketing experience and epidemiologic studies, should be summarized. The procedures used to obtain this information should be described.

3. Animal Data. Summarize the animal data that is relevant to human safety. Any additional studies that are planned should be described, and the implications of any important findings for labeling should be discussed.

4. Analysis of Adverse Effect Dose-Response Information. An integrated analysis of all data from animal and human studies that affect the dose-response and blood level-response relationships of adverse events, the method of dose selection, the choice of dose interval, and dosing recommendations in the package insert should be performed. The effect of demographics and other patient characteristics on the dose-response relationships should be explored.

C. The third section should include Drug-Drug Interactions.

1. Interactions that are predictable on the basis of the pharmacologic activity of the drug, and potential interactions with drugs that are likely to be coadministered with the drug should be identified.

2. All data regarding drug-drug interactions should be summarized, including those obtained from formal pharmacokinetic and pharmacodynamic studies and clinical trials. Listings of the number of patients exposed to each concomitant drug should be developed and each of these groups examined for any unusual adverse events.

3. Drug-Demographic and Drug-Disease Interactions. The information from pharmacokinetic and pharmacodynamic studies as well as clinical trials should be analyzed in the same way as were done to determine drug-drug interactions.

4. Pharmacologic Properties Other Than the Property of Principal Interest. The available preclinical and clinical data that describe other pharmacologic properties of the drug should be discussed with emphasis placed on those actions that are related to unwanted effects and drug-drug interactions.

5. Long-Term Adverse Effects. Available long-term data (6 months or more) should be summarized, and any delayed adverse effects should be noted.

D. The fourth section should include Withdrawal Effects.

Specific studies of withdrawal effects, and any data concerning withdrawal effects observed in the clinical studies should be summarized.

9. Drug Abuse and Overdose Information

For drugs with a potential for abuse, information relating to the abuse of the drug as well as a proposal for scheduling under the Controlled Substances Act should be included. If the drug is structurally or pharmacologically related to a drug with abuse potential, but no studies have been done, the reasons why these studies are considered unnecessary should be included. Information related to overdose, as well as antidotes, other treatments, and measures to be taken in the case of overdose must also be provided.

10. Integrated Summary of Benefits and Risks of the Drugs

Generally, the integrated summary of benefits and risks is a brief summary of the main evidence for effectiveness and the main adverse experiences noted during the clinical program. These data should show that under the conditions of the labeling, the benefits of the drug exceed the risks. In some situations, such as the ones listed below, a more detailed discussion is warranted.

Presence of a severe known or potential human toxicity
A positive carcinogenicity finding
Marginal effectiveness or inconsistent results

A limited data base
Use of a surrogate end point

N. Other NDA Requirements

1. *Safety Updates*

After the NDA application has been filed with the FDA, sponsors are required to update their submissions at regular intervals with safety data that may affect the contraindications, warnings, precautions, and adverse reactions sections of the labeling.

These updates must be submitted 4 months after the original NDA submission, after receipt of an approval letter, and at other times when requested by the FDA. The exact content of these filings will depend on the number and types of studies conducted after the NDA filing. The information to be in the safety update may include the following:

1. Table of new investigators organized in the same manner as the list of investigators in the clinical data section of the NDA.
2. Additional extent of exposure. If the total exposure has changed substantially, it may need to be reanalyzed.
3. Demographies of additional exposure. The demographies of the additional patients exposed to the drug should be provided. Again if the total exposure has substantially changed, demographies may have to be reanalyzed.
4. The adverse experiences reported in the new investigations should be analyzed and displayed as outlined in the integrated summary of safety. If the extent of exposure has increased substantially, the analyses should be performed including both the new data and the data submitted in the NDA.

   If the new data lead to conclusions that are different from those in the original NDA submission, possible causes of the differences should be examined, and complete reports of the safety aspects of the studies should be provided.
5. Clinical laboratory data should be provided in the same manner as was discussed for the adverse experiences.
6. Adverse event data from other sources including the world literature should be included.
7. If new data are extensive and improve the ability to conduct analyses of drug-response, drug-drug, drug-demographic, or drug-disease interactions, they should be provided, along with any relevant information on pharmacologic properties, long-term adverse effects, or withdrawal effects.

O. The Integrated Clinical/Statistical Report

The clinical and statistical information and analyses from a clinical trial should be integrated into a single report. For uncontrolled studies, studies of conditions for which no claim is made in the application, or other studies being provided in the application in support of safety only, the effectiveness results may be presented more briefly than described here; complete safety analyses should always be performed. For all analyses, tables, and figures, the patient population from which these data were generated should be clearly identified.

The contents of a fully integrated clinical/statistical report should include the following information:

1. Title Page

   This includes the protocol numbers of other study identifiers, the title of the study, name and address of the investigator(s), identification of the individuals who prepared the report, dates of initiation and completion of the study, as well as the date of the final report.
2. Table of Contents
3. Identity of Test Materials, Lot Numbers, etc.
4. Introduction

   This is a brief statement of the purpose and design of the study. Background information on the drug and any special features or aims of the study should be described.
5. Study Objectives

   The specific objectives of the study, including any secondary objectives and subgroup hypotheses should be explained; whether the objectives were preplanned or formulated during or after completion of the study should be stated.
6. The Investigational Plan
   a. Overall Design and Plan of the Study

      In this section, the overall study plan and design as well as the organization of the study are discussed. This should include the patient populations, methods of blinding, assignment of patients to treatment groups, duration of study periods, and other pertinent information; any changes in the protocol or conduct of the study after the study was initiated should also be described.
   b. Description and Discussion of the Design and Choice of Control Group(s)

      Discuss specific control(s) chosen; any known or potential problems associated with the study design as well as its suitability for the support of specific claims should be included.
   c. Study Population

In this section, the study population together with the inclusion and exclusion criteria should be discussed. Information to support the suitability of the population for use in the study, as well as a rationale for the sample size should be provided.

d. Method of Assigning Patients to Treatment

The means for assigning patients to treatment should be described. A copy of the randomization schedule should also be provided as an appendix to the study.

e. Dose Selection

The procedures for assigning the doses of the test drug and control agent(s) should be described.

f. Blinding

The specific procedures used for blinding should be described, including the circumstances under which the blind can be broken, and the person who has access to the patient codes. If blinding was found to be unnecessary or unfeasible, this as well as the implications should be discussed.

g. Effectiveness and Safety Variables Recorded and Data Quality Assurance

The specific efficacy and safety parameters measured in the study and when they were conducted should be discussed.

Describe the means for obtaining adverse experience data. If a rating scale is used for assessing efficacy or safety, the criteria for point assignments should be provided.

h. Compliance with Dosing Regimens

i. Appropriateness and Consistency of Measurements

j. Criteria for Effectiveness

The primary measurements and end points used to determine effectiveness should be clearly specified.

k. Concomitant Therapy

l. Removal of Patients from the Study or Analysis

Predetermined reasons for removing patients from therapy should be described along with follow-up procedures. If decisions about evaluability are made after blinding is broken, this should be noted and any potential bias discussed.

7. Statistical Methods

The planned sample size and the formula for sample size and power calculations should be provided.

a. Statistical and Analytical Plans

Discuss the planned statistical analyses and any changes made while the study was conducted. Emphasis should be placed on which analyses and comparisons are planned, not on the specific statistical techniques to be used.

b. Interim Analyses

The frequency and nature of any planned interim analyses and any circumstances under which the study may be terminated should be discussed. Include any statistical adjustments to be used because of interim analyses.

8. Disposition of Patients Entered

All patients who entered the study should be provided for. Reasons for discontinuation of those who did not complete the study and information on whether the blind was broken at the time the patient left the study should be included.

9. Data Sets Analyzed

a. Which patients are included in the efficacy and safety analyses should be precisely defined. If the analyses are based on a subset of the patients with data, an "intent-to-treat" analysis of all randomized patients should also be performed.

b. Demographic and Baseline Features of Individual Patients and Comparability of Treatment Groups

Critical demographic and baseline characteristics of the patient population and any other factors that might affect response should be presented; comparability of treatment groups for each relevant characteristic should be documented. If there is an effectiveness subset of patients as well as an "intent-to-treat" population, this should be done for both groups. In a multicenter study, comparability should be assessed by center, and the centers should be compared.

10. Efficacy Results

a. Analysis of Measures of Effectiveness

The treatment groups should be compared by use of the analyses that were outlined in the protocol. For multicenter studies, the information presented should give a clear picture of the results at each site.

b. Statistical/Analytical Issues

Important features of the analysis, including adjustments for interim analyses, handling of dropouts, and missing data, should be included. Information on the selection and adjustments for covariate or prognostic factors such as baseline measurements, demographics, and concomitant therapy, together with the results of analyses, should be included.

c. Multicenter Studies

In a multicenter study, the results from the individual centers should be presented, and tests for treatment-by-center interactions should be performed.

d. Multiple End Points

e. Use of an "Efficacy Subset" of Patients

One should be careful to assess the effects of dropping patients with available data from analyses. An "intent-to-treat" analysis including all available data from all patients should be performed.

f. Active-Controlled Studies

When an active control is used, the data should be compared with previous studies of similar design that included a placebo and the active control to document the response of the active control. Confidence limits for the difference between the drug and the active control and/or power to detect a difference between the treatments also should be included to document the capability of the study to distinguish between the two treatment groups.

g. Examination of Subgroups

h. Tabulation of Individual Response Groups

Individual response and other relevant study information should be tabulated and included in the appendix.

i. Analysis of doses administered and, if possible, dose-response and blood level-response relationships.

j. Analysis of Drug-Drug and Drug-Disease Interactions

k. Depending on the nature of the study, by-patient displays of data may also be useful to include in the appendix.

11. Safety Results

a. Extent of Exposure

The extent of exposure of subjects to the study medications should be described. Generally, this is presented in categories such as 1 day or less, 2 days to 1 week, 1 week to 1 month, etc. The duration of posttreatment follow-up should also be included. Generally, all patients who received at least one dose of study medication are included in the safety analysis. If this is not the case, an explanation should be provided.

b. Adverse Experiences

- i. The overall adverse events in the study should be discussed in a narrative form and supported by tabulation and analyses. Information on both the test drug and the control should be presented.
- ii. All new adverse events should be displayed and analyzed in tables listing each reported event, number of patients in each treatment group experiencing the event, and rates of occurrence. These may be divided by body system, severity, and relationship to study drug.
- iii. Adverse events that are related should be grouped together by means of a standard adverse reaction dictionary such as WHO or COSTART.
- iv. The analysis of adverse event rates should be used to compare

rates in treatment and control groups. For the more common adverse events, one also may want to look at the relationship to dose, duration of treatment, demographics, or other baseline features.

v. Listings of all adverse events for each patient by investigator and treatment group should be provided in an appendix. It is suggested that this information include the following:
  - Patient identifier
  - Age, sex, race, weight
  - Treatment and dose
  - Onset
  - Duration
  - Intensity
  - Action taken
  - Outcome
  - Relationship to test drug

vi. Display and analysis of deaths and dropouts due to adverse events and other adverse events that are serious or potentially serious should be included. All patients who left the study prematurely because of adverse experiences (including laboratory abnormalities) should be listed. All deaths and potentially serious adverse experiences also should be listed, and a description of the event and relationship to the study drug should be included. Summary information and narrative discussions of the data should be included in the report, and the listings should be provided in an appendix.

c. Clinical Laboratory Evaluation

A narrative discussion and summary tables should be included in the report, and the data listings should be provided in an appendix.

i. Tabular listings should be provided for all safety-related laboratory tests carried out on each patient. Abnormal values should be identified.

ii. List each abnormal value.

iii. Evaluate each laboratory parameter. This section should include mean or median values over time as well as individual patient changes. Individual marked abnormalities should be highlighted.

12. Summary and Conclusions

The efficacy and safety data should be briefly summarized. Any inconsistencies or limitations of the study should also be addressed.

13. Appendices

The appendices generally include the following information:

a. Cross references of all pertinent materials
b. Protocol, sample case report form, and amendments
c. Publication
d. Investigator'(s) curriculum(a) vitae
e. Randomization scheme and codes
f. Documentation of statistical analyses
g. Patient data listings

P. Samples, Methods Validation, and Labeling

The *Guidelines for Submitting Supportive Analytical Data for Methods Validation in New Drug Applications* provides specific directions for this section.

Samples should not be submitted to the FDA with the application. The reviewing chemist will contact the applicant and provide the laboratory address(es) where the samples should be sent. The applicant should prepare four representative samples in sufficient quantity to permit the FDA to perform each test described in the application three times to determine whether the drug substance and the drug product meet the specifications given in the application and whether the assay methodologies work in the FDA's hands. The four samples are:

1. Drug product proposed for marketing.
2. Drug substance used in the drug product.
3. Reference standards and blanks.
4. Samples of the finished market package, if requested by the FDA.

Depending on the product, FDA may also request samples of impurities and degradation products.

The archival copy of an application is required to contain copies of the label and all labeling proposed for the drug product.

For draft labeling, the applicant must submit four copies; for final printed labeling, 12 copies should be submitted. When draft labeling is submitted, one copy should be placed in the archival copy. Single copies should be placed in the chemistry, pharmacology, and clinical review sections of the application. When final printed labeling and carton labeling is submitted, one copy should be mounted, bound, and inserted in the archival copy. The remaining 11 copies should be mounted, bound, and submitted in a separate jacket clearly labeled "Final Printed Labeling."

Well-prepared draft labeling can go a long way toward hastening NDA approval. The FDA, if satisfied with the draft labeling, sometimes will bypass the "approvable" letter if the labeling is the only document needed for final NDA approval. This will be done only if editorial or minor modifications, not substantive changes, need to be made in the labeling.

Q. Case Report Forms and Tabulations

The FDA places a great deal of importance on tabulations of patient data, data elements within tables, and CRFs. It is recommended that applicants meet with the FDA personnel of the division that will receive the application to discuss the extent to which tabulations are needed. Alternative modes of data presentation should be reviewed, along with the requirement for special supporting information in selected cases (e.g., the need for ECGs, x-rays, or pathology slides).

Case report forms should be kept as simple as possible by use of checklists, fill-ins, or the recording of specific measurements. Detailed narratives should be used for an investigator's written summary of the study. Complicated CRFs make the preparation of good tabulations more difficult. Where abbreviations or little-used terms are used on tables or graphs, explanations or definitions should be provided for ease of review.

1. Case Report Tabulations

Tabulations of data on individual patients are required from:

The initial clinical pharmacology (phase 1) studies
The "adequate and well-controlled" (phase 2 and 3) studies
The safety data, e.g., side effects, adverse reactions, and laboratory data from all other studies (phase 2 or 3 studies that are not considered adequate and well controlled).

Efficacy data on patients from studies that are not adequate and well controlled need not be tabulated. Applicants should resist the temptation of combining uncontrolled with controlled trials because it "strengthens" the statistics of the data. Studies should be grouped by design, not outcome.

Upon request, the FDA will discuss with the applicant in a pre-NDA conference those tabulations the FDA agrees may be deleted because they are not considered pertinent to a review of the drug's safety and effectiveness. If a circumstance arises in which previously agreed-to deleted material is requested in a tabulation, the request will come from the director of the FDA division responsible for reviewing the application. Any additional tabulations requested by the FDA should be submitted by the applicant within 30 days after receipt of the request.

2. Case Report Forms

The routine submission of copies of all CRFs for each clinical study is no longer required. Unless waived by the FDA, CRFs are required only for:

All patients who died during a clinical study.
Patients who did not complete a study because of any adverse event, whether or not the adverse event is considered drug related by the inves-

tigator or sponsor. This includes patients receiving reference drugs or placebo.

Generally, the FDA also requires complete sets of CRFs for studies the sponsor has designated as adequate and well controlled. It is suggested that this be discussed at the pre-NDA meeting and CRFs for those studies be included in the NDA if requested by the FDA.

It should be clearly understood that for certain drug classes or therapeutic areas, the FDA may request additional CRFs to conduct a proper review. The FDA will designate the critical studies for which CRFs will be required. The director of the FDA division responsible for the review will make any requests to the applicant. In addition, CRFs may be requested if data tabulations are not adequate to convey important information contained in CRFs. All requests for CRFs must be compiled by the applicant within 30 days after receipt of the request.

3. Information Incorporated by References

Applicants may incorporate by reference any information previously submitted in DMFs or other applications. An incorporation by reference should be made in that segment of the application in which the information referenced would ordinarily appear.

References should be identified by name, reference number, volume, and page number in the FDA's records where the information can be found. If an applicant incorporates by reference information to the FDA by another person, the applicant should obtain and include in the application a written statement from that person authorizing the reference.

R. Review Copy

Each of the technical sections in the review copy must be separately bound in its own particular color folder as previously discussed. Each technical section should include an index (table of contents) for the section, a copy of the application form (FDA 356h), a copy of the cover letter, any letters of authorization, and a copy of the application summary. These items should be separated by tabs clearly marked as to the information being submitted.

VI. THE ABBREVIATED NEW DRUG APPLICATION (ANDA) (21 CFR 314.55)

The archival copy of an **ANDA** may include a cover letter and is required to contain the following data and information:

Application form—21 CFR 314.50(a)
Index—21 CFR 314.50(b)
ANDA suitability statement
Chemistry, manufacturing, and controls—21 CFR 314.50(d) (1)
Human pharmacokinetics and bioavailability—21 CFR 314.50(d) (3)
Samples and labeling section—21 CFR 314.50(e)
Other information—21 CFR 314.50(g)

The FDA will file (i.e., accept an ANDA) only if it has made a finding that an ANDA is suitable for a drug product.

A. Review Copy

Each of the technical sections in the review copy of the ANDA must be separately bound as previously described and must include a copy of the application form.

B. Guidelines

Guidelines have been developed to assist applicants in preparing ANDAs. These include:

1. Format and content for the following sections:
    a. Application summary
    b. Chemistry, manufacturing, and controls section
    c. Nonclinical pharmacology and toxicology section
    d. Human pharmacokinetics and bioavailability section
    e. Clinical and statistical section
    f. Microbiology section
2. Guideline for postmarketing reporting of adverse drug reactions
3. Guideline for the submission in microfiche of the archival copy of an application
4. Guideline for submitting supporting documentation for the manufacture of drug substance
5. Guideline for submitting supporting documentation for the manufacture of finished dosage forms
6. Guideline for submitting supportive analytical data for methods validation in new drug applications
7. Guideline for submitting supporting documentation for stability studies of human drugs and biologics
8. Guideline for packaging

VII. SUMMARY

This and the preceding chapters are merely a guide to the preparation of an NDA. All sponsors and applicants must become familiar with the rules and procedures the FDA follows in reviewing highly detailed, complex, and voluminous documents. It takes the collective efforts of many talented people in a drug company to compile the data necessary to fulfill the requirements of an NDA and to put them together in a package that can be reviewed. It then takes the skills of FDA personnel to examine, review, and rule on the submitted data to ensure that the NDA meets all the requirements of the Federal Food, Drug and Cosmetic Act. It is hoped that the NDA format and the publication of guidelines delineating content requirements will help produce more consistently high-quality applications by providing guidance in new areas, especially those that have proved to be problems in the past.

APPENDIX A. NDA REVIEW GUIDE

1. General Information

The name of the drug and the associated descriptive features, especially if changes occurred during the investigational process.

2. Chemistry, Manufacturing and Controls

Review any problems with clinical implications, especially if a variety of dosage forms were used.

3. Pharmacology

Pharmacodynamics, pharmacokinetics, and toxicology should be reviewed thoroughly, especially where equivocal results occurred.

4. Clinical Background

- Prior history of similar human studies and results
- Literature references (pertinent to the drug studied)
- Related INDs and NDAs

5. Clinical Studies

- Controlled studies.
- Review trials for objective of the study.
- Rationale for the study.
- Experimental design, especially designs that may be considered novel or unusual.
- Procedures.
- Safety considerations (and comparative safety considerations).
- Efficacy considerations (and comparative efficacy considerations).

- Results of statistical consultation.
- Results of the study.

6. **Scientific Conclusions**

- What will the studies support?
- What claims for labeling and advertising?
- What are the deficiencies/problems in any study that may need to be reflected in the labeling?

7. **Regulatory Conclusions**

- Impact on proposal labeling, especially comparative claims
- Side effects
- Alert reports
- Adverse experiences; comparison to placebo or competitive products
- Warnings; any severe or life-threatening (boxed)
- Uncontrolled studies; safety data
- An accounting for investigators
- Need for postmarketing studies—for duration, for specialty groups (e.g., children or elderly)
- Labeling review with a careful evaluation of each section for basic content, clarity, and full disclosure (review 21 CFR 201.56 and 201.57).

APPENDIX B. DATA FOR THE NDA

Tables 1 through 4 at the end of this chapter provide lists of the types of information that must be gathered, evaluated, categorized, and tabulated for use in preparing the NDA. By no means all inclusive, the references should help the reader respond to the intricacies of the application and help confirm the review and examination of all items that may be of interest in the development of the NDA.

Because each therapeutic or diagnostic situation is different, there can be no predetermined measure of the amount of data that must be submitted with each application. Therefore, an NDA should be submitted only when the sponsor is convinced and satisfied that the safety and efficacy of the drug product have been established to the degree required by the FDA to permit appropriate use by medical practitioners for the prevention or alleviation of human suffering.

Table 1 Data for NDA

Chemistry	Quality control and process engineering
Patient situation	Drug substance
Analogs	Reference standard
Choice of salt or form	Development of tentative/final assay methods
Contract manufacturer of chemical	Chemical and physical stability testing
Development of laboratory process	Supply methods/IND
Preparation of bulk	Feasibility run/clinical supplies
Process description-IND	Manufacturing data/NDA
Develop process phase 1 & 2 bulk	Control data/NDA
Product bulk phase 1 & 2	Quality assurance in place
Preparation of tagged materials	
Develop manufacturing process	**Manufacturing**
Produce bulk phase 3	Engineering of production lines
Process description-NDA	Routine production/drug product

Table 2 Data for NDA

Nonclinical pharmacology	Toxicology and biopharmaceutics
Pre-IND study	Acute toxicity
Screening	Range Finding
- cardiovascular	Subacute toxicity
- respiratory-visceral	
- CNS	
- endocrinology	Pre-IND studies
Summary	- Microbiology
Publication	- Immunology
Phase 1 & 2 clinical support	- Chemotherapy
Update summary	- Biochemistry
Support phase 3 Clinical	Data/IND
Clinical feedback	Reproduction (seg. I, II, III)
Summary reports/NDA kinetics	Chronic toxicity
	Carcinogenicity data
	Metabolism (animal, human)
	Interaction studies
Labeling information	Summary reports/NDA

Table 3 Data for NDA

Pharmacy and packaging	**Medical research**
Pre-IND information	Preclinical brochure
	Prepare phase 1 & 2
Phase 1	- plans
Dosage forms	- protocols
Laboratory formula sheets	- case report forms
Processing instructions	Demonstrate safety
Short-term stability for IND	Demonstrate effectiveness
Clinical studies phase 1 & 2 dosage forms	FDA contact
Phase 2 dosage forms	Clinical biopharmaceutical studies
Packaging	Summary phase 1 & 2
Clinical supplies phase 3	Select dosage
Long-term stability	Update brochure
Scale-up and production	Phase 3
Feasibility run	- plans
Stability report/data	- protocols
Summary report/NDA	- case report forms
	FDA contact—end of phase 2 meeting
	Phase 3 studies
	Summary report/NDA
	First draft of package insert
	Pre-NDA review
	Monitor summaries
	Review investigator summaries

Table 4 Data for NDA

Science information, regulatory affairs, information monitor	**Statistical and science information sciences**
Review investigator brochure	Prepare case report form
Review phase 1 & 2	
- plans	Format for tabulations
- protocols	
- case report forms	Automation of data handling methodology
Regulatory compliance	Statistics phase 1 & 2
Labeling preparation	Statistics phase 3
FDA contact—end of phase 2 meeting	Special statistical analysis
Review protocols	Special printouts
Review summary	- adverse experiences
Review brochure/update	- patient summaries
FDA contact—pre-NDA meeting	- investigator summaries
Review statistical evaluation phase 3	- laboratory summaries
Assemble and integrate NDA—archival and review copies	Literature summaries and reprints Translation of foreign materials
Final NDA summary and package insert	
Advertising and promotion review	

REFERENCES

1. Temple R. The NDA rewrite. Presentation at the Fifth Annual Arnold Schwartz Memorial Program, New York, 1984.
2. Lavy NW. Factors influencing clinical research success. In: MJ Finkel, ed. Principles and Techniques of Human Research and Therapeutics, vol. XI. Mount Kisco, NY: Futura, 1976, pp. 133–142.

6

The Biologic License Application (BLA)

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I. INTRODUCTION

The 1990s has brought us the era of FDA regulatory reform. The law, the regulations, and the agency itself have undergone a tremendous change. The Center for Biologic Evaluation and Research (CBER) has undergone some of the most significant changes. As former FDA Commissioner David Kessler, M.D. had wanted, the drug and biologic approval processes have become very similar. Gone forever is the two-license system, the responsible head designation, and all the many other things that had made the biologic approval process so unique and distinct and so different from drugs.

All this change has brought us to the new CBER and the single application and single license era. The Biologic License Application (BLA) has replaced the Product License Application (PLA) and the Establishment License Application (ELA). Gone are many CBER regulations, replaced now by CDER regulations. This is not so foreign considering that in the early 1970s, FDA had declared and defined all biologic products as drugs, thus allowing FDA to regulate biologic products under two laws: the Federal Food, Drug and Cosmetic Act and the Public Health Service Act.

In the BLA, a biologic product sponsor submits thousands of pages of nonclinical and clinical data, chemical and biologic information, and product manufacturing descriptions. The submission must allow CBER reviewers to make three principal determinations:

1. Whether the biologic is safe and effective in its indicated use and whether the benefits of using the product outweigh the risks

2. Whether the biologic's proposed labeling is appropriate
3. Whether the methods used in manufacturing and quality control are adequate to preserve the biologic's identity, strength, quality, potency, and purity

II. A SHORT HISTORY OF THE LICENSING PROCESS FOR BIOLOGICS

Given that government regulation of biologics has historically focused on the product manufacturing process, it is not surprising that the ELA has a considerably longer history than the PLA. Congress was first spurred to regulate the biologic industry in 1901, when 10 children died after being treated with diphtheria antitoxin that had been contaminated with tetanus.

But in establishing regulatory controls to prevent the contamination of the biologic products of that day—essentially vaccines and antitoxins—Congress had to work within the limitations of existing scientific knowledge and technology. At that time, it was difficult, and in many cases impossible, to identify component parts of any biologic product or to detect the presence of pathogens and other contaminants. The absence of sensitive assays for identifying, and purification processes for separating, biologic contaminants left researchers to use crude immunological and in vivo tests.

This situation was complicated by the fact that the production processes for traditional biologics, usually involving human or animal extracts, were highly susceptible to contamination. The reality that contaminants were often infectious materials or toxins amplified the threat.

At that time, regulating production facilities seemed to be the only mechanism likely to control the quality of biological products. Consequently, Congress passed the Biological Control Act of 1902, which required that biologics in interstate commerce be manufactured in facilities holding a valid establishment license. Interestingly, the statute failed to mandate government review or sanction of the products themselves, only that the establishments manufacturing and preparing the products meet specific criteria and permit the inspection of their facilities.

Not until 1944, when Congress modified the statute, did federal law require the licensure of products as well. Under the revision, both establishments and products must "meet standards designed to insure the continued safety, purity, and potency of such products, prescribed in regulation."

For the next 52 years, the dual licensure procedure was the centerpiece of biologic regulation in the United States. Because biologic products are difficult to characterize structurally, complete descriptions of the production processes and manufacturing facility have been regarded as essential to the control of product manufacture. Thus, the difficulty in the biologic product characterization has been the most important scientific reason for CBER's continuing reliance on the ELA.

In 1994, the FDA began to look for ways to lesson regulatory burdens on industry. Because of this initiative, CBER took steps to modernize its regulatory program to reflect scientific and technologic advances. Although these reforms affected virtually every aspect of biologic regulation, they signaled the end of CBER's dual licensing system.

In 1996, CBER began to consolidate the dual licensing system that had been in place since 1944. Specifically, with a final regulation published in May 1996, CBER established that categories of highly characterized products would require only the submission of a single license application, a BLA, and the granting of a single license for marketing. In justifying this change, CBER stated "that technical advances have greatly increased the ability of manufacturers to control and analyze the manufacture of many biologic\biotechnology-derived products. Methodologies are now available to characterize these products, allowing the product to be more clearly evaluated by end-product testing." The end of the dual licensing era had arrived, at least for certain categories of products. For these products, gone forever was the ELA.

In November of 1997, President Clinton signed the Federal Food, Drug and Cosmetic Modernization Act of 1997. One section of this law required that all biologic products be licensed under the single licensing system. With his signature, President Clinton put an end to the CBER's dual licensing system.

Since the signing of this law, CBER has issued guidances for the submission of the "Chemistry, Manufacturing, and Control Information and Establishment Description" for all categories of biologic products. By the end of 1999, the single licensing system should be fully implemented. As all these changes are being implemented, CBER is also preparing for the next-phase computerized license applications. Numerous guidance documents already have been issued by CBER to address the computerized format.

III. INTRODUCTION TO BLAs: CONTENT AND FORMATTING REQUIREMENTS

The Center for Biologics Evaluation and Research had established no specific formatting requirements for PLAs. This was in sharp contrast to new drug applications, for which the agency has detailed formatting standards. Although the lack of a uniform PLA format has caused industry concern in the past, significant differences between various license applications, and biological products themselves, had slowed efforts to standardize PLA formats.

However, CBER did make available a series of PLA application forms that identify basic PLA submission requirements for different types of products.

Most of these PLA forms applied to blood products, vaccines, and other, more traditional, biologic products. The center has not yet developed forms for many of the more advanced biologic products, including new therapeutic products.

In most cases, PLA forms identified submission requirements by posing a series of questions that the sponsor had to answer in the application. Essentially, the lack of a standard format was a function of the diversity of questions posed by different PLA forms. Often, applicants based the formats of their applications on the sequence of questions specified in the PLA form.

Given the absence of a standard PLA format and the advent of the new single license system, CBER in 1996 published a new draft BLA form (Form FDA-3439). Subsequent to this, during 1997, CBER and CDER issued the harmonized application form—Form FDA 356(h). This form represented a standard format for all drug, biologic, antibiotic, and generic drug products. Hence the harmonized form. The form is titled "Application To Market A New Drug, Biologic, Or An Antibiotic Drug For Human Use" (see page 163).

The Form FDA 356(h) is a 1-page form that is 2-sided. The first side is administrative, providing information on the applicant as well as the product. The back side identifies the content requirements for a BLA application. However, because the form is to be used for generic drug and antibiotic products also, not all 19 sections are applicable to BLAs. In addition to the BLA application form, federal regulations, CBER guidelines, and points-to-consider documents developed for specific product classes also offer information on BLA application submission requirements. In general terms, the BLA consists of reports of all investigations sponsored by the applicant, and all other information pertinent to an evaluation of the product's safety, effectiveness, potency, and purity.

IV. THE CONTENTS OF THE BLA

As stated above, the 356(h) form is a 1-page, 2-sided document; the front side contains administrative information about the applicant and product, and the back side includes content and format requirements for the BLA application. In addition to this form, a cover letter should always accompany any FDA submission.

Addressed in the following pages are the Form FDA 356(h), the cover letter, and all 19 sections of the BLA application (see p. 163).

Cover letter
Application form—Form FDA 356(h)
Section 1-Index
Section 2-Labeling

Section 3-Summary
Section 4-Chemistry section
Section 4a-Chemistry, manufacturing, and controls information
Section 4b-Samples
Section 4c-Methods validation package
Section 5-Nonclinical pharmacology and toxicology
Section 6-Human pharmacokinetics and bioavailability
Section 7-Clinical microbiology
Section 8-Clinical data section
Section 9-Safety update report
Section 10-Statistical section
Section 11-Case report tabulations
Section 12-Case report forms
Section 13-Patent information
Section 14-Patent certification
Section 15-Establishment description
Section 16-Debarment certification
Section 17-Field copy certification
Section 18-User fee cover sheet
Section 19-Other

Before each section is addressed individually, it is worth emphasizing the importance of the application form (Form FDA 356(h)), the cover letter, and the first three sections. Applicants frequently overlook their significance, perhaps because they are not technical sections or because they often are not seen as critical. For several reasons, this is unfortunate. First, these items and sections are among the few in the entire application that each member of the BLA licensing committee receives for review. Additionally, because these sections, particularly the cover letter and the summary, provide information in an abridged form, they are also likely to be read thoroughly by each committee member. The sections are also important because they represent, in some ways, the applicant's "opening argument" for its product. In the summary section, for instance, the sponsor is granted what some view as a greater editorial license not available in any of the BLA's other sections. Such views aside, the sponsor must use these sections to frame and build its case for the new biologic's safety and effectiveness.

A. Cover Letter

Although not required by regulation, the cover letter is requested by FDA to accompany all FDA submissions. In the cover letter, sponsors often supply the FDA with much of the basic administrative information requested about the

BLA application (e.g., sponsor name and address, etc.). The cover letter should provide at least seven types of information:

1. Name and Address of Sponsor and Others

The cover letter should provide the name and address of the sponsor. If the sponsor is using outside contractors or manufacturing sites at other locations, the cover letter should provide their addresses and identify their functions.

2. Product Name

The sponsor should provide the trade and generic names of the product in the cover letter.

3. Reason for the Submission

The cover letter should identify the type of application being submitted (e.g., original submission, supplement, amendment, etc.).

4. Information Contained in the Submission

In the cover letter, the sponsor should identify what information is contained in the submission. Identify the total number of volumes being submitted and contents of each volume (e.g., volumes 50–150 contain clinical information).

5. Agreements with FDA

If the sponsor has reached any agreements with CBER relevant to the BLA, this information should be included in the cover letter. Given the quantity of applications under review within CBER and the fact that such agreements often are made months in advance, reviewers might not recall the existence or details of such agreements. Reviewer turnover is another factor that makes recounting these agreements good working practice.

6. Other Documents Relating to the Submission

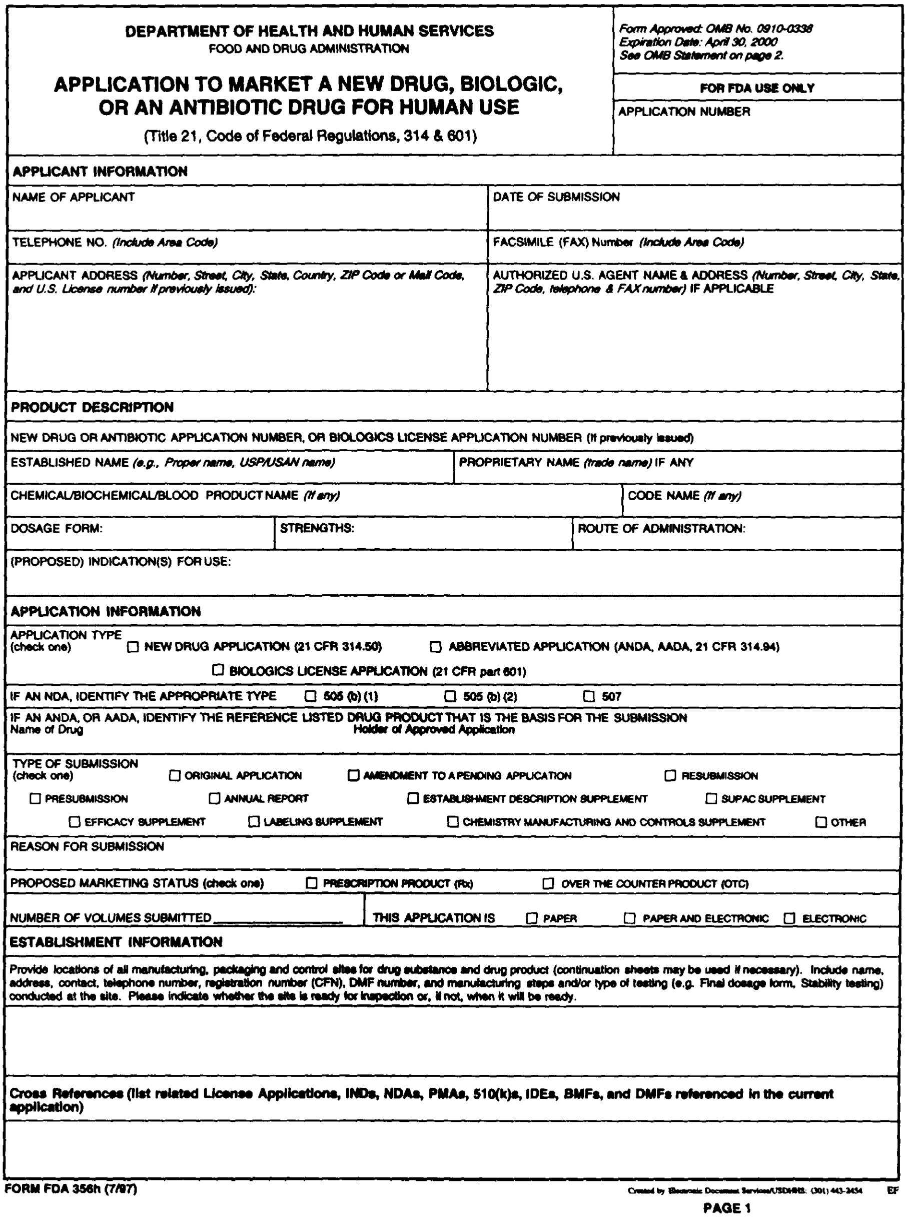
To alert CBER reviewers to other documentation that must be referenced during the BLA review, the sponsor should note in the cover letter other documents associated with the application, such as INDs, BLAs, and master files.

7. Special Circumstances

Alert CBER of any special circumstances surrounding the product. For example, the product may be an orphan drug product. Because of the circumstances relating to the product, CBER may pay special attention to the submission and shepherd it through the licensure process more quickly.

8. *Priority Review*

If your product has been classified for priority review, remind CBER of the fact in the cover letter.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY
APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
DATE OF SUBMISSION
TELEPHONE NO. *(Include Area Code)*
FACSIMILE (FAX) Number *(Include Area Code)*
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)
ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*
PROPRIETARY NAME *(trade name)* IF ANY
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
CODE NAME *(If any)*
DOSAGE FORM:
STRENGTHS:
ROUTE OF ADMINISTRATION:
(PROPOSED) INDICATION(S) FOR USE:

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug
Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED ____________
THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

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This application contains the following items: *(Check all that apply)*

	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, *including, but not limited to the following:*

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.
Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number ( )

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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Hubert H. Humphrey Building, Room 531-H
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Washington, DC 20201

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Please DO NOT RETURN this form to this address.

INSTRUCTIONS FOR FILLING OUT FORM FDA 356h

APPLICANT INFORMATION This section should include the name, street address, telephone and facsimile numbers of the legal person or entity submitting the application in the appropriate areas. Note that, in the case of biological products, this is the name of the legal entity or person to whom the license will be issued. The name, street address and telephone number of the legal person or entity authorized to represent a non-U.S. Applicant should be entered in the indicated area.

PRODUCT DESCRIPTION This section should include all of the information necessary to identify the product that is the subject of this submission. For new applications the proposed indication should be given. For supplements to an approved application please give the approved indications for use.

APPLICATION INFORMATION If this submission is an ANDA or an AADA, this section should include the name of the approved drug that is the basis of the application and identify the holder of the approved application in the indicated areas.

TYPE OF SUBMISSION should be indicated by checking the appropriate box:

Original Application = a complete new application that has never before been submitted;

Amendment to a Pending Application = all submissions to pending original applications, or pending supplements to approved applications, including responses to Information Request Letters;

Resubmission = a complete response to an action letter, or submission of an application that has been the subject of a withdrawal or a refusal to file action;

Presubmission = information submitted prior to the submission of a complete new application;

Annual Report = periodic reports for licensed biological products (for NDAs Form FDA-2252 should be used as required in 21 CFR 314.81 (b)(2));

Establishment Description Supplement = supplements to the information contained in the Establishment Description section (#15) for biological products;

SUPAC Supplement = all supplements submitted under a SUPAC guidance;

Efficacy Supplement = submissions for such changes as a new indication or dosage regimen for an approved product, a comparative efficacy claim naming another product, or a significant alteration in the patient population; e.g. prescription to Over-The-Counter switch;

Labeling Supplement = all label change supplements required under 21 CFR 314.70 and 601.12 that do not qualify as efficacy supplements;

Chemistry, Manufacturing and Controls Supplement = all manufacturing change supplements as required by 21 CFR 314.70, 314.71, 314.72 and 601.12; except SUPAC supplements;

Other = any submission that does not fit in one of the other categories (e.g., Phase IV response). If this box is checked the type of submission can be explained in the **REASON FOR SUBMISSION** block.

REASON FOR SUBMISSION This section should contain a brief explanation of the submission, e.g., "manufacturing change from roller bottle to cell factory" or "response to Information Request letter of 1/9/97."

NUMBER OF VOLUMES SUBMITTED Please enter the number of volumes, including and identifying electronic media, contained in the archival copy of this submission.

This application is
☐ Paper ☐ Paper and Electronic ☐ Electronic
Please check the appropriate box to indicate whether this submission contains only paper, both paper and electronic media, or only electronic media.

ESTABLISHMENT INFORMATION This section should include information on the locations of all manufacturing, packaging and control sites for both drug substance and drug product. If continuation sheets are used please indicate where in the submission they may be found. For each site please include the name, address, telephone number, registration number (Central File Number), Drug Master File number, and the name of a contact at the site. The manufacturing steps and/or type of testing (e.g. final dosage form, stability testing) conducted at the site should also be included. Please indicate whether the site is ready for inspection or, if not, when it will be ready. Please note that, when applicable, the complete establishment description is requested under item 15.

CROSS REFERENCES This section should contain a list of all License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs that are referenced in the current application.

Items 1 through 19 on the reverse side of the form constitute a check list that should be used to indicate the types of information contained within a particular submission. Please check all that apply. The numbering of the items on the checklist is not intended to specify a particular order for the inclusion of those sections into the submission. The applicant may include sections in any order, but the location of those sections within the submission should be clearly indicated in the Index. It is therefore recommended that, particularly for large submissions, the Index immediately follow the Form FDA 356h and, if applicable, the User Fee Cover Sheet (FDA Form 3397).

The CFR references are provided for most items in order to indicate what type of information should be submitted in each section. For further information, the applicant may consult the guidance documents that are available from the Agency.

Signature The form must be signed and dated by an agent or official authorized by the applicant to represent the applicant to the Agency. The agent's typed name, title, address and phone number should be provided in the areas indicated.

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B. Application Form FDA 356(h)

The application form (Form FDA 356[h]) serves several functions. First, it is an administrative document providing CBER with information on the applicant, product, and application. Second, it is a legal contract binding the applicant, contractors, suppliers, and physicians to FDA laws and regulations. The applicant is already bound by FDA laws and regulations, but many contractors, suppliers and physicians are not. Contrary to what many believe, physicians are not regulated by FDA or FDA laws and regulations. Physicians are licensed by states and controlled in this manner. The Food and Drug Administration will not accept an application unless the application form is signed.

C. Item 1—Index

Perhaps the single most important factor in a BLA's "user friendliness" is the speed and ease with which a reviewer can find information during the review process. Because it can influence the speed and efficiency of the review as well, the manner in which the applicant indexes BLA information is of central importance. Applicants can use the format below for indexing the BLA:

Item	Description	Volume/page
2	Labeling	1.010

The "Item" column refers to the item number listed on the back of the Form FDA 356(h) application. The "Description" column identifies the subject of the item number listed on the back of Form FDA 356(h). In the "Volume/Page" column, the number to the left of the decimal point represents the application's volume number, whereas the number to the right refers to the page within that volume containing the relevant section. In practice, the index is typically far more detailed, with each item broken down into specific subparts.

D. Item 2—Labeling Section

This section encompasses the initial draft labeling submitted with the BLA and the final printed labeling that is submitted just prior to licensure. Labeling includes the immediate container label, carton label, insert, and user instructions. The container and package labels should permit accurate identification of the contents, whereas the package insert should summarize the essential information required for the product's safe and effective use. These data should be accurate, balanced, informative and nonpromotional. When possible, the information should be based on data obtained from the product's use in humans.

E. Item 3—Summary Section

In many ways, the BLA summary is a condensed version of the entire application. The summary serves as a guide to the full application, explaining the application's intent-to-establish the biologic's safety and effectiveness for a particular indication, and highlighting the studies and evidence supporting the biologic's safety and effectiveness.

The summary's importance cannot be overstated. In this section, the sponsor can state and argue its case for the product's approval. A well-prepared summary includes a straightforward description of the product and its manufacturing technology, testing data, nonclinical data, clinical data, and adverse and beneficial effects. Such a summary can build CBER's confidence in the applicant, the validity of the BLA's information, and the product itself. In addition, because the summary is one of the few sections reviewed by all members of the BLA licensing committee, it can be pivotal in establishing a foundation for product approval.

The summary, ordinarily 50–200 pages in length, provides reviewers in each review area, and other agency officials, with a good general understanding of the product and of the application. The summary should discuss all aspects of the application and should be written with about the same level of detail required for publication in refereed scientific and medical journals and should meet the editorial standards generally applied by these journals. To the extent possible, data in the summary should be presented in tabular and graphic forms. The summary should comprehensively present the most important information about the product and the conclusions to be drawn from this information.

The summary should avoid any editorial promotion of the product, i.e., it should be a factual summary of safety and effectiveness data and a neutral analysis of these data. The summary should include an annotated copy of the proposed labeling, a discussion of the product's benefits and risks, a description of the foreign marketing history of the drug (if any), and a summary of each technical section.

1. Summary Format

Description of drug and formulation
Annotated draft insert
Product pharmacologic class
Scientific rationale for use of product
Clinical benefits
Foreign marketing history
CMC summary
    7a. Drug substance
    7b. Drug product
    7c. Stability
    7d. Investigational summary (listing of batches used in the clinical studies)

Nonclinical summary
    8a. Pharmacology
    8b. Toxicology
Human pharmacokinetics and bioavailability
Microbiological summary
Clinical summary
Benefit/risk relationship

F. Item 4—Chemistry Section

The BLA's chemistry section is composed of three parts:

1. Chemistry, manufacturing, and controls information
2. Samples
3. Methods validation package

In most aspects, the BLA is essentially a PLA that features a new chemistry section in which the sponsor provides some, but not nearly all, of the data and information previously submitted in the PLA/ELA. The remaining information formerly provided in the PLA/ELA will be reviewed during CBER's preapproval inspection.

The Center for Biologics Evaluation and Research has issued guidance documents identifying the CMC information that will be required in BLAs for each class of product.

1. Chemistry, Manufacturing, and Controls Information

This section is composed of five parts:

Drug Substance
Drug Product
Investigational Formulation
Environmental Assessment
Method Validation

a. Drug Substance

Many of CBER's guidelines address the information required for the drug substance. This indeed does make a lot of sense, because the drug substance is the active moiety, the item that produces the pharmacologic response in humans. The information required by CBER for the drug substance is identified below.

Description and Characterization. This section should provide a clear description of the physical and chemical properties of the synthetic drug substance, including the chemical structure, primary and subunit structure, molecular weight, and molecular formula. If the product is cellular based, the source of the cell line and all the pertinent physical and chemical properties necessary to characterize the cell line should be listed. The biologic name or chemical name, including the USAN name, should also be provided.

A description and the results of all the analytical testing performed on the manufacturer's reference standard lot and qualifying lots to characterize the drug substance should be included. The section should provide information from specific tests regarding the identity, purity, stability, and consistency of manufacture of the drug substance. All test methods should be fully described and the results provided.

A description and results of all relevant in vivo and in vitro biologic testing performed on the manufacturer's reference standard lot to show the potency and activity of the drug substance should be included. Results of relevant testing performed on lots other than the reference standard lot and that might have been used in establishing the product's biologic activity should also be provided.

Manufacturer. The application should include the name, address, FDA registration number, and other pertinent organizational information for each manufacturer performing any portion of the manufacture or testing operations for the drug substance. A brief description of the operations performed at each location, the responsibilities conferred upon each party by the applicant, and a description of how the applicant will ensure that each party fulfills its responsibilities should be included.

For each manufacturing location, the BLA should include a floor diagram that indicates the general facility layout. This diagram need not be a detailed engineering schematic, but should be a simple drawing that depicts the relationship of the subject manufacturing areas, suites, or rooms to one another, and should indicate other uses made of adjacent areas that are not the subject of the application. This diagram should be clear enough to permit the reviewer to visualize the flow of the drug substance's production and to identify areas or room "proximities" that may be of concern for particular operations (e.g., segregation of animal facilities).

This section should provide a comprehensive list of all additional products to be manufactured or manipulated in the areas used for the product. The applicant should indicate in which rooms the additional products will be introduced and the manufacturing steps that will take place in the room. An explanation should be given as to whether these additional products will be introduced on a campaign basis or concurrently during production of the product under review.

For all areas in which operations for the preparation of cell banks and product manufacturing are performed, including areas for the handling of animals used in production, the following information regarding precautions taken to prevent contamination or cross-contamination should be provided:

Air quality classification of rooms or areas in which an operation is performed, as validated and measured during operations

A brief, narrative description of the procedures and facility design features for the control of contamination, cross-contamination, and containment (air pressure cascades, segregation of operations and products, etc.)

General equipment design description (e.g., does design represent an open or closed system or provide for a sterile or nonsterile operation?)

A description of the in-process controls performed to prevent or to identify contamination or cross-contamination.

Method(s) of Manufacture. This subsection should include the following information on raw materials and reagents: (a) a list of all components used in the manufacture of the drug substance, and their tests and specifications, or a reference to official compendia, (b) a list with tests and specifications of all special reagents and materials used in the manufacture of the drug (e.g., culture media, buffers, sera, antibiotics, monoclonal antibodies, preservatives), and (c) a description of the tests and specifications for materials of human and animal source that may potentially be contaminated with adventitious agents (mycoplasma, bovine spongiform encephalopathy [BSE] agent for bovine-derived products, and other adventitious agents of human origin).

A complete visual representation of the manufacturing process in flow chart format should be included. This flow chart should indicate the step in the process, the equipment and materials used, and the room where the operation is performed, and should provide a complete list of the in-process controls and tests performed on the product at each step. The diagram should also include information, including a descriptive narrative, on the methods used to transfer the product between steps (i.e., sterile, SIP connection, sanitary connection, open transfers under laminar flow units, etc.).

If animals are used in the production process, the subsection should include descriptions of the sources of animals, the method of creating and the genetic stability of transgenic animals, adventitious agent screening and quarantine procedures used to assure that the animals are appropriate for use in manufacturing, animal husbandry procedures, and veterinary oversight. For more guidance, use the appropriate CBER guidelines and "Points to Consider" documents.

For monoclonal antibodies, the submission should include a detailed description of the development of the monoclonal antibody, including characterization of the parent cells, donor history for human cells, immunogen, immortalization procedures, and cell cloning procedures.

For recombinant DNA products, including rDNA-derived monoclonal antibodies produced from cellular sources, the guideline states that the submission should include a detailed description of the host cell and expression vector systems and their preparation, including the following:

1. *Host Cells.* A description of the source, relevant phenotype, and genotype for the host cell used to construct the biologic production system. The results of the characterization of the host cell for phenotypic and genotypic markers, including those that will be monitored for cell stability, purity, and selection, should be included.

2. *Gene Construct.* A detailed description of the gene that was introduced into the host cells, including both the cell type and the origin of the source material, should be provided, along with a description of the method(s) used to prepare the gene construct and a restriction enzyme digestion map of the construct. The complete nucleotide sequence of the coding region and regulatory elements of the expression construct, with translated amino acid sequence, should be provided, including annotations designating all important sequence features.

3. *Vector.* Detailed information regarding the vector and genetic elements should be provided, including a description of the source and function of the component parts of the vector.

4. *Final Gene Construct.* A detailed description should be provided of the cloning process that resulted in the final recombinant gene construct.

5. *Cloning and Establishment of the Recombinant Cell Lines.* Depending on the methods to be used to transfer a final gene construct or isolated gene fragments into its host, the mechanism of transfer, the copy number, and the physical state of the final construct inside the host cell should be provided. In addition, the amplification of the gene construct, if applicable, the selection of the recombinant cell clone, and the establishment of the seed should be completely described.

The method of manufacture section should also include a subsection on the cell seed lot system, which should address three items:

6. *Master Cell Bank.* In most cases, the cell bank used to manufacture the biologic will derive from a larger group of cells called the master cell bank, or MCB. A detailed description of its preparation and testing as outlined in the ICH guideline should be provided. The MCB should be described in detail, including the methods, materials, reagents, and media used, date of creation, quantity of the MCB, in-process controls, and storage conditions. This section should also provide the results of the characterization of the MCB for identity and purity using phenotypic markers and the testing of the MCB for endogenous and adventitious agents.

7. *Master Working Cell Bank.* A detailed description of the working cell bank, or WCB and the cell line used to produce the biologic product must be provided. The production of the WCB should be described in detail.

8. *End of Production Cells.* A detailed description of the end of production cell's (EPC's) characterization that demonstrates that the biologic production system is consistent during growth should be included. This section should

also include test results showing that the EPC is free from contamination by adventitious agents.

Lastly, the cellular sources subsection of the methods of manufacture section must include a detailed description of the process of inoculation, cell growth, and harvesting. The stages of cell growth should be described carefully, including the selection of the inoculum, scale-up for propagation, and established and proposed (if different) production batch size.

The CMC Section of the BLA must also provide a details of the purification and downstream processing, including a rationale for the chosen methods. In addition, the precautions taken to ensure the containment and prevention of contamination or cross-contamination should be identified. If applicable, the section should indicate the multi-use nature of areas and equipment (e.g., campaigning versus concurrent manufacture; dedicated versus shared equipment) used for these procedures.

Finally, the methods of manufacture section must provide a completed (executed) representative batch record of the drug substance's production process.

Process Controls. This CMC subsection should provide information in two key areas:

1. *In-Process Controls.* A description of the methods used for in-process controls (e.g., those involved in fermentation, harvesting, and downstream processing) should be included. A brief description of the sampling procedures and test methods used should be provided. For testing performed at significant phases of production, the criteria for accepting or rejecting an in-process batch should be specified.

2. *Process Validation.* A description and documentation of the validation studies should be included. If the process was changed or scaled up for commercial production and this involved changes in the fermentation steps, the revalidation of cell line stability during growth should be described, as in the previous section, and the data and results provided. A description and documentation of the validation studies for the cell growth and harvesting process that identify critical parameters of routine products should be submitted. Similarly, description and documentation of the validation of the purification process should be included. Finally, the subsection should describe and document the validation studies or any processes used for media sterilization and inactivation of cells prior to their release to the environment (if such inactivation is required).

A summary report, including protocols and results, should be provided for the validation studies of each critical process or factor that affects the drug substance specifications for:

Propagation
Harvest

Purification
Inactivation
Microbiology
Aseptic processing

3. *Reference Standard.* If an international reference standard (WHO, NIBSC) or compendial reference standard (USP) is used, the applicant should submit the citation for the standard and a certificate of analysis. If an inhouse working reference standard is used, a description of the preparation, characterization, specifications, and testing and results should he provided.

4. *Specifications/Analytical Methods.* The specifications and tests sufficient to assure the identity, purity, strength, and potency of the drug substance, as well as its lot-to-lot consistency, should be submitted. Certificates of analysis and analytical results for at least three consecutive qualification lots of the drug substance should be provided. Lastly, this subsection should include a discussion of the impurity profiles, with supporting analytical data, as well as profiles of variants of the protein drug substance (e.g., cleaved, aggregated, deamidated, oxidized forms) and non–product-related impurities (e.g., process reagents and cell-culture components).

5. *Container/Closure System.* A description of the container and closure system and its compatibility with the drug substance should be submitted. The section should include detailed information concerning the supplier and the results of compatibility, toxicity, and biologic tests. Alternatively, a drug master file (DMF) may be referenced for this information.

6. *Drug Substance Stability.* This subsection should include a description of the storage conditions, study protocols, and results supporting the stability of the drug substance. For more specific information, the FDA guideline "Stability Testing for Drug Substances and Drug Products" should be consulted.

b. Drug Product

Although less detailed than those for the drug substance, the requirements of the guideline for the drug product are also grouped into eight areas.

Composition. This subsection should include a tabulated list of all components with their unit dose and batch quantities for the drug product or diluent in accordance with the "Guideline for Submitted Documentation for the Manufacture of and Controls for Drug Products." The compositions of all ancillary products that might be included in the final product should be provided.

Specifications and Methods for Drug Product Ingredients. If the information is not specified in the drug substance section, this section should include a description of tests and specifications for all active ingredients. The specifications for all ancillary products included in the drug product should be provided as well. Information on all excipients, including process gases and water, should be included and should include a list of compendial excipients (and their citations) and tests and specifications for noncompendial excipients.

Manufacturer. The names and addresses of all manufacturers involved in the manufacture and testing of the drug product, including contractors, and a description of their respective responsibilities should be included. A list of all other products (i.e., research and development, clinical, or approved) made in the same rooms should be provided as well.

Methods of Manufacture and Packaging. A complete description of the manufacturing process of the formulated bulk and finished drug product, including a description of sterilization operations, aseptic processing procedures, lyophilization, and packaging procedures. Along with this narrative, the subsection should include a flow chart indicating each production step, the equipment and materials used, the room or area where the operation is performed, and a listing of the in-process controls and tests performed on the product at each step. This flow diagram or narrative should also include information on the methods for transferring the product between steps.

Specifications and Test Methods for Drug Product. This subsection should include the sampling procedures for monitoring a batch of finished drug product. The specifications used for the drug product and a description of all test methods selected to assure the identity, purity, strength, or potency, as well as the lot-to-lot consistency of the finished product, should be provided.

Container/Closure System. A description of the container and closure system and its compatibility with the drug product should be submitted. Detailed information concerning the suppliers, their addresses, and the results of compatibility, toxicity, and biologic tests should be included. Alternatively, a DMF can be referenced for this information.

Microbiology. Information should be submitted as described in FDA's "Guidance for Industry in the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products."

Drug Product Stability. A description of the stability protocols and results supporting the product's stability (expiration date and storage condition) should be provided. Stability data supporting the proposed shelf-life of reconstituted drug products and for all labeled dilutions also should be included. The stability protocol provided should include the following:

Potency
Physiochemical measurements that are potency-indicating
Moisture, if applicable
pH, if applicable
Sterility or control of bioburden
Viability of cells

Pyrogenicity
General safety

A plan for an ongoing stability program should be included. This should comprise the protocol to be used, the number of lots to be entered each year, and an indication of how the lots will be selected.

c. *Investigational Product/Formulation*

This section should consist of a discussion of any differences in formulation, manufacturing process, or site between the clinical trial materials and commercial production batches of the drug substance and drug product.

d. *Environmental Assessment*

If an environmental assessment is required, it should be prepared as outlined in the federal regulations (21 CFR 25). It should include a description of the action being considered and address all components involved in the manufacture and disposal of the product. A statement of exemption under a categorical exclusion may be provided if applicable.

e. *Method Validation*

Although the guideline states that the CMC section must include a method validation section, it does not specify submission requirements. Rather, the guideline refers applicants to the FDA's "Guideline for Submitting Samples and Analytical Data for Methods Validation."

As noted above, the CMC subsection is only one of three elements comprising the BLA's chemistry section. The other two subsections address samples and the methods validation package.

f. Samples

Before a biologic product is marketed, the FDA will want to validate the sponsor's characterization methods for both the biologic substance and the finished product. Therefore, at some point during the review process, CBER may request any or all of the following: a biologic substance sample, a finished product sample, and the sponsor's reference standards. According to FDA regulations, the sponsor must submit "four representative samples of each sample in sufficient quantity to permit FDA to perform three times each test described in the application to determine whether the drug substance and drug product meet the specifications given in the application."

g. Methods Validation Package

The methods validation package provides information that allows FDA laboratories to validate all of the analytic methods for both the drug substance and the drug product. Specifically, the package consists of three copies of the analytical methods and related descriptive information in the CMC section for the drug substance and drug product.

According to the FDA's "Guideline for Submitting Samples and Analytical Data for Methods Validation," the methods validation package should include: a statement of composition; new drug substance and product specifications; certificates of analysis for each sample submitted; and the regulatory analytical methods. Detailed information in the package should include: a tabular listing (lot, identity, etc.) of all samples to be submitted; a listing of all proposed regulatory specifications; information supporting the integrity of the reference standard; a detailed description of each method of analysis; and information supporting the suitability of the methodology for the new drug substance and the dosage form.

G. Item 5—Nonclinical Pharmacology and Toxicology Section

The BLA must describe all nonclinical pharmacology and toxicology studies conducted on the biologic product. These nonclinical laboratory studies include those submitted in the IND, those submitted during clinical investigations, and new nonclinical studies not previously submitted. The Center for Biologics Evaluation and Research reviews these studies to evaluate their adequacy and comprehensiveness and to ensure that there are no inconsistencies or inadequately characterized toxic effects. The application also should include information on studies not performed by the sponsor but of which the sponsor has become aware (e.g., studies in published literature).

Content requirements for the nonclinical pharmacology and toxicology section of license applications are not defined specifically in CBER regulations or guidelines. As it does in many other instances, the BLA form refers biologics' sponsors to regulations for the pharmacology/toxicology section of an NDA. These regulations ask for descriptions, with the aid of graphs and tables, of animal and in vitro studies with the drug, including the following:

1. Studies of the pharmacologic actions of the drug in relation to its proposed therapeutic indication and studies that otherwise define the pharmacologic properties of the drug or are pertinent to possible adverse effects.
2. Studies of the toxicologic effects of the drug as they relate to the product's intended clinical uses, including, as appropriate, studies assessing the product's acute, subchronic, and chronic toxicity, and studies of toxicities related to the product's particular mode of administration or conditions of use.
3. Studies, as appropriate, of the effects of the drug on reproduction and on the developing fetus.

4. Any studies of the absorption, distribution, metabolism, and excretion of the drug in animals.
5. For each nonclinical laboratory study subject to Good Laboratory Practice (GLP) regulations, a statement that it was conducted in compliance with such regulations or, if not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

For each study identified above, the applicant should include a summary, followed by a full report including data and statistical analyses. Summaries assist FDA reviewers in obtaining a brief analysis of the study.

Along with the summaries and full reports, the applicant should provide an integrated report. Such a report integrates results from all pharmacology studies in a single, comprehensive analysis. Sponsors should provide a similar report for the toxicology information.

H. Item 6—Human Pharmacokinetics and Bioavailability Section

Although few biologic products will have bioavailability data, most will have pharmacokinetics data that must be provided in the BLA. As it does for the pharmacology and toxicology section, Form 356(h) refers biologics' applicants to the regulatory requirements specified for an NDA human pharmacokinetics and bioavailability section, as follows:

1. A description of each of the bioavailability and pharmacokinetic studies of the drug in humans, including a description of the analytical and statistical methods used in each study and a statement with respect to each study that it either was conducted in compliance with IRB regulations or was not subject to the regulations, and that it was conducted in compliance with the informed consent regulations.
2. If the application describes in the chemistry, manufacturing, and controls section specifications or analytical methods needed to assure the bioavailability of the drug product or drug substance, or both, a statement in this section of the rationale for establishing the specifications or analytical methods including data and information supporting the rationale.
3. A summary discussion and analysis of the pharmacokinetics and metabolism of the active ingredients and the bioavailability or bioequivalence, or both, of the drug product.

More detailed recommendations on the development and presentation of this section are available from CDER's Guidelines.

I. Item 7—Clinical Microbiology

This section is required only for anti-infective products. Because these products affect microbial, rather than clinical, physiology, reports relevant to the product's in vivo and in vitro effects on the target microorganisms are critical for establishing product effectiveness.

Current regulations require that an application's anti-infective section include microbiology data characterizing: (a) the biochemical basis of the drug's action on microbial physiology, (b) the antimicrobial spectra of the drug, including the results of in vitro nonclinical studies to demonstrate concentrations of the drug required for effective use, (c) any known mechanisms of resistance to the drug, including results of any known epidemiologic studies to demonstrate prevalence of resistance factors, and (d) clinical microbiology laboratory methods (for example, in vitro sensitivity discs) needed for effective use of the product.

More specific guidance on developing the microbiology component of the BLA is available from a CDER Guideline entitled "Guideline for the Format and Content of the Microbiology Section of an Application."

J. Item 8—Clinical Data Section

The applicant's clinical data section is a particularly critical element of the filing. Included in this section are the safety and effectiveness data pivotal to the FDA's decision-making process. The clinical data section is also likely to be the applicant's most complex and voluminous section.

The clinical data section of a BLA should consist of the following basic elements:

1. A description and analysis of each clinical pharmacology study of the biologic, including a brief comparison of the results of the human studies with the animal pharmacology and toxicology data.
2. A description and analysis of each controlled clinical study pertinent to the biologic's proposed use, including the protocol and a description of the statistical analyses used to evaluate the study. If the study report is an interim analysis, this must be noted and a projected completion date provided. Controlled clinical studies that have not been analyzed in detail for any reason (e.g., because they have been discontinued or are incomplete) should be provided, including a copy of the protocol and a brief description of the results and status of the study.
3. A description of each uncontrolled clinical study, a summary of the results, and a brief statement explaining why the study is classified as uncontrolled.
4. A description and analysis of any other data or information relevant

to an evaluation of the product's safety and effectiveness obtained or otherwise received by the applicant from any foreign or domestic source. This should include information derived from clinical investigations (i.e., including controlled and uncontrolled trials of uses of the product other than those proposed in the application), commercial marketing experience, reports in the scientific literature, and unpublished scientific papers.

5. An integrated summary of the data providing substantial evidence of effectiveness for the clinical indications. Evidence is also required to support the dosage and administration section of the labeling, including the dosage and dose interval recommended and modifications for specific subgroups of patients (e.g., pediatrics, geriatrics, patients with renal failure).

6. An integrated summary of all available information about product safety, including pertinent animal data, demonstrated or potential adverse effects of the drug, clinically significant drug-drug interactions, and other safety considerations, such as data from epidemiologic studies of related drugs. This subsection should also include a description of any statistical analyses performed in reviewing safety data, unless it is included elsewhere in the clinical section.

7. If the drug has the potential for abuse, a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the Controlled Substances Act. A description of any studies related to overdosage is also required, including information on dialysis, antidotes, or other treatments, if known.

8. An integrated summary of benefits and risks of the biologic, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling.

9. A statement noting that each human clinical study was conducted in compliance with IRB and informed consent regulations. If the study was not conducted according to these regulations, the applicant must state this fact and the reasons for noncompliance.

10. If a sponsor has transferred any obligations for the conduct of a clinical study to a contract research organization (CRO), a statement providing the name and address of the CRO, identifying the clinical study, and providing a list of the obligations transferred. If all obligations regarding the conduct of the study have been transferred, a general statement of this transfer—in lieu of a listing of the specific obligations transferred—may be submitted.

11. If original subject records were audited or reviewed by the sponsor in the course of monitoring any clinical study to verify the accuracy of the case reports submitted to the sponsor, a list identifying each clinical study so audited or reviewed.

Although there is no required format for the clinical section, I recommend formatting the section in the following manner:

1. Integrated summary of benefits and risks
2. Integrated summary of safety
3. Integrated summary of effectiveness
4. Phase 3 adequate and well-controlled studies used for the determination of product safety and effectiveness
5. All other phase 3 studies
6. Phase 2 studies
7. Human pharmacology studies not included in item 6
8. Other information

This format allows CBER to review the most important information first.

K. Item 9—Safety Update Report

As implied by its title, the safety update report is not submitted with the original BLA, but is submitted in the form of updates at specific points in the application review process. Applicants must submit safety update reports 4 months after the BLA submission, after receipt of a complete response letter, and other times requested by CBER. In these reports, the sponsor must update the pending BLA with new safety information learned about the product that may reasonably affect the labeling statements in the contraindications, warnings, precautions, and adverse reactions sections. The updates must include the same types of information from clinical studies, animal studies, and other sources, and must be submitted in the same format as the BLA's integrated safety summary. They must also include case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event.

L. Item 10—Statistical Section

The statistical section of the BLA is essentially the same as the clinical data section, inasmuch as the clinical reports include all the statistical analyses. With this information, the statisticians can assess the validity of key analyses and evidence supporting the biologic's safety and efficacy.

The statistical section is composed of the following information:

1. A list of investigators supplied with the drug or known to have investigated the drug, INDs under which the drug was studied, and NDAs submitted for the same drug substance
2. An overview of the clinical studies conducted
3. Item 8, the clinical data section
4. Statistics used for the integrated summaries of benefits/risks, safety and effectiveness, and rationale for use of such statistical methods

M. Item 11—Case Report Tabulations Section

During the FDA's most recent revision of its NDA regulations, the agency declared that "an efficient agency review of individual patient data should be based primarily on well-organized, concise data tabulations. Reviews of the more detailed patient case report forms should be reserved for those instances where a more complete review is necessary."

The agency advises sponsors to meet with FDA to discuss the extent to which tabulations of patient data in clinical studies, data elements within tables, and case report forms are needed. Such discussions can also cover alternative modes of data presentation and the need for special supporting information (for example, ECGs, x-rays, or pathology slides).

According to agency regulations and guidelines, the case report tabulations section must provide:

1. Tabulations of the data from each adequate and well-controlled study (phase 2 and phase 3)
2. Tabulations of the data from the earliest clinical study
3. Pharmacology studies (phase 1)
4. Tabulations of the safety data from all other clinical studies

Federal regulations add that these tabulations should include the data on each patient in each study, except that the applicant may delete those tabulations that the agency agrees, in advance, are not pertinent to a review of the drug's safety or effectiveness.

N. Item 12—Case Report Forms (CRF) Section

As stated above, FDA does not require the routine submission of patient CRFs. Rather, the forms are required only for: (a) patients who died during a clinical study, and (b) patients who did not complete a study because of any adverse event, whether or not the adverse event is considered drug related by the investigator or the sponsor.

The FDA may request that the sponsor submit additional CRFs that the agency views as important to the drug's review. Typically, the agency will request all CRFs for the pivotal studies. In doing so, the agency's reviewers will attempt to designate the critical studies for which CRFs are required about 30 days after the application's receipt. If a sponsor fails to submit the CRFs within 30 days of the FDA's request, the agency may view the eventual submission as a major amendment and extend the review period as appropriate.

O. Item 13—Patent Information Section

Applicants must provide information on any patent(s) on the product for which approval is sought or on a method of using the product. Such information is included in the "Orange Book" (*Approved Drug Products with Therapeutic Equivalence Evaluations*). All approved (licensed) drug products are listed in this book.

P. Item 14—Patent Certification Section

Applicants must provide a patent certification or statement regarding any relevant patents that claim the listed drug or any other drugs on which investigators seeking approval of the application relied, or that claim a use for the listed or other drug.

According to the FDA's "Guideline on Formatting, Assembling, and Submitting New Drug and Antibiotic Applications," the patent certification and patent information should be attached to the application form in the submission.

Q. Item 15—Establishment Description Section

The CBER guidance documents state that item 15 of the BLA should be composed of three principal sections that provide information describing establishment standards and Good Manufacturing Practices (GMP) controls in place for the manufacture of the product. The three principal sections are (a) General Information, (b) Specific Systems, and (c) Contamination/Cross-Contamination Issues.

1. General Information

For each manufacturing location, the BLA should include a floor diagram indicating the general production facility layout. Each diagram or accompanying narrative should include product, personnel, equipment, waste, and air flow for production areas; an illustration or indication of which areas are served by each air-handling unit; and air pressure differentials between adjacent areas.

2. Specific Systems

a. Water Systems

The BLA should include information for systems used in the production of water for manufacturing and rinsing of product-contact equipment. This subsection should include a general description of water system(s), a validation summary, and information on the routine monitoring program.

b. Heating, Ventilation, and Air Conditioning (HVAC) Systems

This subsection must also include a general system description, a validation summary, and information on the routine monitoring system.

c. Computer Systems

This section should contain information on computer systems that control critical manufacturing processes. The developer of the system should be identified and information provided also should include a brief description of procedures for changes to the computer system. This section also should contain a validation summary for each of these systems and a certification that an IQ and OQ have been completed.

3. Contamination/Cross-Contamination Issues

For dedicated equipment, the sponsor must provide a brief description of the cleaning procedures and reagents used, as well as certification that cleaning validation for removal of product residuals and cleaning agents has been successfully completed. For shared equipment, including that used for processing the cells of more than one patient, BLA sponsors must provide a description of the cleaning procedures and reagents used, the rationale for the chosen procedures, and a report describing validation procedures, sampling methods, and analytical methods. The section must also provide information on containment features, including segregation and containment procedures for areas, manufacturing operations, personnel, equipment, and waste materials designed to prevent product contamination.

In general, the BLA must provide CBER reviewers with an overview of the manufacturing facility and its operations regarding the product.

R. Item 16—Debarment Certification Section

Since mid-1992, the FDA has required that all NDAs and BLAs include a certification that the applicant did not and will not use the services of individuals or firms that have been debarred by the FDA. Under the Generic Drug Enforcement Act of 1992, the FDA is authorized to debar individuals convicted of crimes relating to the development, approval, or regulation of drugs or biologics from providing any services to applicants. The statute requires that applications for drug products (including biologic products) include a certification that the applicant did not and will not use in any capacity the services of any person debarred in connection with such application.

S. Item 17—Field Copy Certification Section

Since 1993, United States-based NDA sponsors have been required to submit a "field" copy of the NDA's chemistry, manufacturing, and controls section, application form, and summary directly to the relevant FDA district office for use during the preapproval manufacturing inspection. The applicant has also been required to certify in its NDA that an exact copy of the chemistry, manufacturing, and controls section contained in the application has been forwarded to the relevant FDA district office. In the past, CBER itself conducted preapproval biologics' inspections and no such certification was required in the BLA. With the advent of Team Biologics and the introduction of the field force to biologic inspections, it is now advisable to talk to the application division the sponsor is dealing with to get the current requirements.

T. Item 18—User Fee Cover Sheet Section (Form FDA 3397)

Since January 1994, the FDA has required every new drug application and biologic license application to include a copy of the User Fee Cover Sheet. This form provides information that permits the FDA to determine whether the application is subject to user fees and, if so, whether the appropriate fee for the application has been submitted. The FDA will not start a review of an application unless verification of receipt of the user fee has been obtained.

U. Item 19—Other Information Section

The BLA applicant may provide in this section any other information that may help the agency evaluate the safety and effectiveness of the product.

V. AMENDING THE LICENSE APPLICATION

During the review of the BLA, the FDA is likely to request additional information to address unresolved issues regarding the original submission. A response to such a request is generally referred to as an amendment. A change to any unapproved application is called an amendment (IND, BLA, NDA). The content of a BLA amendment will depend on the nature of CBER's information request. The format used in this submission is similar to that used for the original BLA submission. The cover letter for the amendment should be titled: "Amendment to BLA ____________." In the cover letter, the applicant should clearly identify the purpose of the amendment and the contents of the submission. The amendment should be paginated in a manner that will allow CBER to locate the section of the BLA in which the amendment should be incorporated.

VI. SUPPLEMENT TO THE ORIGINAL BLA

Although amendments are submitted to update or modify an unapproved BLA, supplements are submitted to modify approved license applications. The holder of an approved BLA may seek to change its manufacturing methods, expand the product's indication, or make other changes that reflect new technology or make its product or processes more competitive. Compared with companies holding approved NDAs for drug products, biologic licensees traditionally have had considerably less latitude in making minor changes to labeling or manufacturing processes without first obtaining FDA approval through a supplemental application.

In April 1995, however, CBER implemented a new policy creating a three-tier reporting and approval mechanism for postapproval manufacturing and facility changes. Under this policy, only significant changes—those in categories II and III—will require the submission of a supplement. Only category III changes—important proposed changes in manufacturing methods—will require FDA preclearance before implementation.

Because category II and III changes can be expected throughout a product's lifecycle, supplementing the BLA becomes an ongoing process. Supplement-related activity is particularly high as a company refines, scales up, and streamlines its manufacturing operation. Content requirements for supplemental BLAs will depend on the nature of the proposed change. In general, the applicant provides new data and information sufficient to support the modification.

VII. ASSEMBLING AND SUBMITTING THE BLA

Whether submitting an original BLA, an amendment, or a supplement, the applicant should follow these requirements:

1. The BLA should be properly indexed and paginated for ease of review. Each volume should be no more than 2 inches thick, bound on the left side of the page, and printed on standard U.S. paper (8.5″ × 11″). The front cover of each volume should specify the name of the applicant, the name of the product, and the BLA number (if known). The lower right-hand corner of each volume should read: "This submission: 'Volume _ of _ volumes.'" The upper right-hand corner should read "Volume _."

2. Applicants must submit two copies of the BLA to CBER (most likely the CBER division will ask for additional copies). The copies may be hand delivered or mailed. If the applicant hand delivers the BLA, the sponsor should bring an extra copy of the cover letter with the shipment so that the letter may be date-stamped upon delivery to the FDA's Document Control Center. This letter provides evidence that the document was submitted to the FDA. If forwarded by standard mail service, the BLA shipment should include a letter of instructions with a document stating that the BLA submission has been received by the FDA. The FDA document control person will sign the document, place

it in a stamped return envelope provided by the sponsor, and return it to the company. This document also serves as proof that the BLA was submitted.

Sponsors mailing the BLA should forward the application and all related submissions to the following address:

Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Suite 200N, HFM-99
Rockville, MD 20852-1448

If the applicant forwards the BLA using a commercial overnight service, a return receipt is provided. In this case, the receipt provides evidence of the BLA's delivery.

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Chemistry, Manufacturing, and Control Requirements of the NDA and ANDA

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I. INTRODUCTION

With the enactment of the FDA Modernization Act of 1997 and the reauthorization of the Prescription Drug User Fee Act of 1992, the drug approval process by FDA is expected to be streamlined further. The Agency is aggressively generating guidance documents to implement the provisions of the statute, so it is up to the drug sponsor to prepare drug submissions that are complete and in a format that will facilitate the review for a rapid approval.

One of the most critical portions of an NDA or ANDA, is item 4 of the Form FDA 356h, the chemistry section. This section, more commonly referred to as CMC, (for chemistry, manufacturing, and controls) is actually subdivided into three subsections: the chemistry, manufacturing, and controls information; samples; and methods validation package. Although the chemistry section of a typical application comprises only 5% of a submission, 25% of FDA guidance documents generated refer to CMC issues, making the chemistry section the most highly regulated part of the application.

Nonclinical and clinical studies are usually completed during the investigational phases of drug development. The final formulation(s) for the product, however, along with the associated analytical methodologies and manufacturing procedures, may not be finalized until the latter part of phase 3 clinical trials. Even with no change in the safety, efficacy, and manufacturing process of a drug in the market, the CMC information on a drug filed with FDA is always updated as long as the company manufactures the drug, whereas clinical and preclinical information are not. Chemistry, manufacturing, and controls issues exist throughout the life cycle of a product.

It is clear that the FDA considers that the CMC section has the potential to significantly decrease NDA review and approval times. In addition to the issuance of guidance documents and CMC initiatives, the regulations permit the submission of item 4 material 90 to 120 days in advance of other sections of the NDA (21 CFR 314.50(d)(iv)) as a further means of expediting the regulatory review process.

Sponsors can help both themselves and the FDA chemistry reviewer by providing sufficient documentation in NDA submissions, particularly regarding the following: (a) methods of synthesis, (b) validation of analytical assay methods for both the drug substance and the finished dosage form(s), (c) container/closure systems, and (d) stability testing. Deficiencies in these key areas also are common causes for the delayed approval of ANDAs. It is important to ensure that the CMC section of an application accurately reflects the actual manufacturing and control processes for the batches to be marketed. This will have great impact on the way the FDA conducts a preapproval inspection for the application. In the pages to follow, recommendations as to what information should be provided in both NDAs and ANDAs will be discussed. Appropriate reference(s) to the applicable guideline(s) will be presented throughout, and Table 1 lists them all for convenience. These guidelines and other pertinent publications issued by FDA can be obtained by mail or through the FDA website (htpp/www/FDA.gov). Differences in the information provided for original and abbreviated new drug filings will also be highlighted.

Table 1 FDA Manufacturing and Controls Guidelines

1. Guideline for the Format and Content of an Application Summary
2. Guideline for the Format and Content of the Chemistry, Manufacturing, and Controls Section of an Application
3. Guideline for Impurities in Drug Substances
4. Guideline for Stability Studies for Human Drugs and Biologics
5. Guideline for Packaging of Human Drugs and Biologics
6. Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances
7. Guideline for Submitting Supporting Documentation for the Manufacture of Finished Dosage Forms
8. Guidelines for Drug Master Files

II. THE NDA SUMMARY

The FDA regulations published February 22, 1995 provide for the preparation of a summary of the NDA, including a condensation of the CMC section. (The "Guideline for the Format and Content of an Application Summary" is available to aid in the preparation of this document.) Properly presented, the summary will provide all of the NDA reviewers a general overview of CMC information for both the drug substance and the drug product. It should be written in sufficient detail and in a style that can meet the editorial standards required for publication in refereed scientific journals. The following subsections detail what should be included in the NDA summary regarding CMC information.

A. The Drug Substance

1. Names

Include the generic name(s), synonyms, and code designation(s) that have appeared in the published literature or in nonclinical or clinical reports being submitted with the application, the proprietary names (brand name or trademark) if known, identification number (e.g., Chemical Abstracts Service [CAS] registry number), and chemical name(s). List the preferred chemical name first, if available. This information can be found in a reference book called *U.S. Adopted Names Council (USAN) Handbook*, if a generic name for the drug substances has been accepted by the Council.

2. Physical and Chemical Properties

Describe the physical and chemical properties of the drug substance. Include, as applicable, appearance, odor, taste, physical form, solubility profile, melting point, boiling range, molecular weight, structural and molecular formulae (Wisswesser line notation), isomers, polymorphs, pK_a pK_b, and pH. A description of the data obtained to elucidate the structure (e.g., spectroscopic characteristics) should also be included.

3. Stability

The results of studies conducted on the drug substance should be summarized and related to the anticipated storage conditions and container/closure system, as well as the retest plan to be used by the sponsor. Statements on whether additional studies are ongoing or planned for the future should be included. Also provide a statement regarding the suitability of the methods used (see the section below on specifications and analytical methods).

4. Manufacture

The name(s) and address(es) of the manufacturer(s), i.e., entity(ies) performing the manufacturing, processing, packaging, labeling, and control operations of the drug substance, must be listed. Include a description of the responsibilities of each manufacturer listed, if more than one is used.

5. Method of Manufacture

Information concerning the method of manufacture may be presented in the form of a flow chart. Supply a brief description of the methods of isolation (e.g., synthetic process, fermentation, extraction, recombinant deoxyribonucleic acid [DNA] procedure) and purification (solvent recrystallization, column chromatography, distillation). Include all synthetic pathways that have been adequately characterized during the investigational stages of drug development.

6. Process Controls

Provide a brief description of the control checks performed at each stage of manufacturing and packaging of the drug substance.

7. Specifications and Analytical Methods

Describe the acceptance criteria and the test methods used to assure the identity, strength, quality, particle size and polymorphic integrity, and purity of the drug substance. The guidelines also indicate that applicable information be provided regarding actual or potential impurities in the drug substance (e.g., by-products, degradation products, antigenic substances, viral contaminants, isomeric components, heavy metal contaminants, extraction solvents, and so forth). As the summary may also be used by the FDA as a reference document in the preparation of the SBA for the product, releasable to the public under the FOI regulations, the information included in the summary regarding impurities should be well considered.

8. Container/Closure System

Describe the characteristics of, and test methods used for the container, the closure, and other component parts. In addition, highlight stability data and any other information that support their suitability for packaging the drug substance.

B. The Drug Product

1. *Composition of the Dosage Form*

A quantitative composition, including the name and amount of each active and inactive ingredient contained in the drug product, should be provided. In addition, an overall description of the dosage form should be included. This should be in sufficient detail to characterize it fully with regard to its type, release properties (i.e., immediate versus sustained or controlled release), and physical characteristics such as shape, color, type of coating, hardness, scoring, and identification marks.

2. *Manufacturer*

The information provided for the manufacturer is analogous to that provided for the drug substance. In this case, however, there are likely to be more facilities listed. Contract packagers, for example, are used frequently for preparing samples or unit dose presentations such as blister packages.

3. *Method of Manufacture*

Briefly describe the manufacturing and packaging process for the finished dosage form(s) of the product (e.g., wet granulation, direct compression, lyophilization).

4. *Specifications and Analytical Methods*

Detail the regulatory specifications and test methods used to assure the identity, strength, quality, purity, and bioavailability of the drug product. The emphasis lies in the assay methodology(ies) used to quantitate the presence of degradation products that assure stability of the drug product.

5. *Container/Closure System*

A description of all the container/closure system configurations for the drug to be marketed should be presented. In addition, stability data and any other information that support the suitability of the container/closure components, including specifications and test methods, should be indicated.

6. *Stability*

The proposed expiration dating period and storage conditions for the product, along with justifications for them based on data obtained from stability studies should be stated.

7. *Test Formulations*

Provide quantitative compositions and lot numbers of each finished dosage form used in nonclinical safety studies, clinical studies, and stability during the investigational phases of development for the drug product. In addition, formulation differences should be explained, and each formulation should be cross-referenced to the study or studies in which it was used.

If these points are clearly and concisely presented, FDA reviewers should have a general understanding of the data and information submitted in the CMC section.

III. CHEMISTRY, MANUFACTURING, AND CONTROLS INFORMATION

This part of an application contains a precise description of the composition, methods of manufacture, specifications, and control procedures for the drug substance and the drug product. It also includes an environmental impact analysis statement for the manufacturing process and for the ultimate use of the drug. (Refer to the "Guideline for the Format and Content of the Chemistry, Manufacturing, and Controls Section of an Application" and 21 CFR 314.50(d)(1), which set forth specific data requirements for this section.)

In preparation of the documents for the CMC section, one of the first items to consider is the selection of a representative batch of the drug substance and the drug product for the NDA. Ideally, the representative drug substance batch selected was used to manufacture the representative drug product batch. This will provide a good and consistent data flow in the CMC section.

A. The Drug Substance

1. *Names*

Include the established (generic) and proprietary (trade) name(s), synonyms (e.g., different names being used for the same drug in other countries), CAS registry number, and code number(s). Most drugs early in their investigation are referred to by some alphanumeric code number until a generic name has been officially approved by the USAN and/or by the WHO as an INN.

2. *Structural Formula and Chemical Name(s)*

The chemical structure(s), molecular formula(e), molecular weight(s), and chemical name(s) should be shown. List all chemical names by which the drug was referred to during its development, and highlight the preferred names assigned by USAN or WHO at the time a generic name was approved.

3. Physical and Chemical Properties

The description provided in this section should include, as applicable, information on the following: (a) organoleptic properties (e.g., appearance, odor, taste); (b) solid-state form (i.e., the preferred crystalline polymorph); (c) solubility profile (limit data to aqueous solubility, pH effect, and at most one or two organic solvents; (d) pH, pK_a, or pK_b; (e) melting and boiling range; (f) specific gravity or bulk density; (g) spectroscopical characteristics such as a specific rotation, refractive index, and fluorescence; and (h) isomeric composition.

4. Proof of Structure

A reference standard batch of the drug substance is used to conduct structure elucidation and confirmation studies.

The elucidation and confirmation of structure should include physical and chemical information derived from applicable analyses, such as: (a) elemental analysis; (b) functional group analysis using spectroscopic methods (i.e., mass spectrometry, nuclear magnetic resonance); (c) molecular weight determinations; (d) degradation studies; (e) complex formation determinations; (f) chromatographic studies methods using HPLC, GC, TLC, GLC; (h) infrared spectroscopy; (j) ultraviolet spectroscopy; (k) stereochemistry; and (l) others, such as optical rotatory dispersion (ORD) or X-ray diffraction.

5. Stability

The results from studies conducted to evaluate the stability of the new drug substance should be described fully. In addition, on the basis of these results, recommendations for the storage conditions and retesting period should be discussed. Data should be submitted from studies of the product stored in open and closed containers analogous to the container in which the drug substance is to be stored and marketed. Generally, manufacturers do these studies in 1- to 5-kg containers fabricated from the same materials used for bulk manufacturing storage.

Other studies, conducted at accelerated storage conditions such as effects of temperatures (freezing, 5° C, 40°–50° C or higher), humidity (75% or greater), and exposure to light should be submitted. These studies generally help define what handling precautions are necessary for bulk storage and during manufacture of the dosage form. The FDA also recommends that studies be conducted on solutions or suspensions of the drug substance to evaluate the effects of acid and alkaline pH, high oxygen and nitrogen atmospheres, and the presence of added substances, including chelating agents and antioxidants.

Indicate the stability-indicating method(s) used to quantitate the drug substance, its impurities, and its degradation products. Define the possible degradation profile of the drug substance. The availability of samples of these impurities/degradation products permits the validation of assay method(s) used to specifically quantitate their levels in the drug substance. Also, either the same method (preferably) or another method of sufficient sensitivity—at least to 0.1% of active drug—must be used to quantitate levels of degradation products.

To avoid or limit problems in this area after submission of the NDA, the validation of analytical methods and the conduct of stability studies should be planned from the initial phases of clinical research. This will provide the type of data approvable by FDA. The reader is directed to the "Guideline for Stability Studies for Human Drugs and Biologics" and the final "ICH Guideline for the Stability of Drug Substance and Drug Product" for assistance in fulfilling this essential requirement.

6. Manufacturer

Under this section, the name and address of each facility (including contract testing laboratories) used in the manufacture and control of the drug substance should be provided. Each building involved in the manufacture of the drug substance should be properly identified by street address and, if appropriate, building number. If more than one building is used, state the part of the operation being carried out in each building. The operations that should be covered include manufacturing, processing, packaging, labeling, and control of the drug substance.

For foreign facilities, manufacturing site facilities, operating procedures, and personnel information must be included in this section. This information can also be available as a type I DMF; therefore, a letter from the DMF holder to the FDA that authorizes the use of applicable data in conjunction with the review of the sponsor's application is sufficient for this section.

7. Method of Manufacture

a. Starting Materials—Specifications and Tests

The starting material(s) used to synthesize the drug substance should comply with FDA's definition of a starting material. For a material to be considered a starting material, it should be: (a) commercially available; (b) a compound whose name, chemical structure, and chemical and physical properties are generally known; (c) described in the literature; and (d) obtained by commonly known procedures (including starting materials extracted from plant or animal sources, and precursors to semisynthetic antibiotics obtained by fermentation procedures). Most of the time, a material will meet several of these criteria. If it does not meet any of them, it probably is not the starting material.

Describe the analytical controls used to ensure the identity, quality, and purity of each batch of starting material. The source of the starting material need not be specified, but may be requested.

b. Solvents, Reagents, and Auxiliary Materials

List all reagents, solvents, and auxiliary materials and a statement of the quality of each material (i.e., USP, NF, ACS, Technical). Describe the specifications and tests used to accept each batch of material. A specific identity test should be included. The need for additional testing depends on the role of the material used in the preparation or isolation of the drug substance.

c. Drug Substance Synthesis

Provide a full description of the method used in the isolation (e.g., synthesis, extraction, fermentation, recombinant DNA procedures) and purification of the drug substance.

The description of the isolation of the drug substance should include a diagrammatic flow chart. Such charts should contain: (a) chemical structures of reactants, molecular weights, and names or code designations, (b) stereochemical configurations, if applicable, (c) structures of intermediates, both in situ and isolated, (d) solvents, (e) catalysts, (f) reagents, and (g) significant side products that may interfere with the analytical procedure or that are toxic.

Describe the processes involved in the synthesis of the drug substance. The description synthesis should include information on the following: (a) pieces of equipment used; (b) quantities of starting material(s) reagents, solvents, catalysts; (c) workup and isolation procedures; (d) reaction conditions such as temperature, pH, and time; (h) purification procedures; (i) manipulative details including addition rate, stirring speed, pressure, and order of addition; and (j) yields (crude and/or purified weight and percent).

The FDA has given approval in the past to the concept of a "pivotal intermediate." This is an analyzed and well-characterized synthetic intermediate that is usually isolated one to two steps before synthesis of the crude final product, but may be obtainable by more than one synthetic route. To obtain approval, material produced by the several routes must be characterized, especially with regard to the identity and level(s) of impurities and the relative qualities of the finished bulk drug substance produced. In addition, a fairly rigorous set of specifications for the intermediate has to be established to assure its ultimate quality by whichever approved route is used in its production (See section on Process Controls below). The benefit to the sponsor is that the level of detail describing the various routes used to make the pivotal intermediate does not have to be as great as normally required. This permits some latitude for implementing modifications to those steps occurring up to the synthesis of the pivotal intermediate without the necessity of receiving prior FDA approval, as long as the quality and impurity profiles of the pivotal intermediate are unaltered from those on file at the FDA.

It also should be noted that FDA may request additional preclinical toxicology studies. This will depend on the degree(s) of difference(s) in the profiles, identities, and the levels of impurities in bulk drug substances produced from the pivotal intermediate made by the various routes of synthesis, and whether the finished drug is intended for short-term or chronic use.

The final steps in the workup, isolation, and purification of the bulk or microencapsulated drug substance should be written in detailed fashion. The description should address the following issues: (a) crude product yield (a range should be given); (b) tests performed on the crude product, preferably including at least one purity test appearing in the finished drug substance specifications; (c) the isolation and purification procedures; (d) alternate purification procedures (polymorphic changes should be considered); (e) yield of purified product (again it is recommended that a range be provided); and (f) evidence that the purification procedure actually improves purity of the crude product (e.g., chromatographic illustrations).

Any alternate method or permissible variation, such as different starting material, reagent, solvent, or conditions, should be reported with an indication of the circumstances under which it will be used, and comparative analytical data should be provided.

d. Antibiotics and Other Products Obtained by Fermentation Processes

Similar information is needed for the preparation, isolation and purification of antibiotics and other drug substances isolated from microbial or cell culture sources. The components of the fermentation media should be defined and specifications established, including, if applicable, a defined degree of purity. The role of each ingredient, if known, should be stated.

Because the specific microorganism cultured is the most critical factor in any antibiotic process, strain identification, including morphologic, cultural, and biochemical characteristics should be performed. The source of the microbial isolate (e.g., soil, air, water), as well as any genetic engineering or mutation procedures should be documented. Microbial deposition should be reported (e.g., American Type Culture Collection or Type Culture Collection of the U.S. Department of Agriculture).

The stability of the cell culture to repeated transfer should be defined, because numerous transfers lead to strain degradation (attenuation). The factors that should be defined are the number of transfers from individual colonies that do not result in a significant decrease of antibiotic production and the proper method(s) and conditions for maintaining an active culture.

The monitoring and control of the fermentation process should be reported in detail. Parameters to be addressed include the media preparation and sterilization, inoculation procedures, and the fermentation process. Provide a detailed description of the media composition, the method for its sterilization (temperature and duration), and the pH after sterilization. The inoculation stage description should include quantity (by volume percent) and age of the inoculum to be used, as well as information on the morphologic stage of the mycelium, if this parameter is controlled. The fermentation stages should be characterized by duration, temperature, pH, aeration rate (volume of air per volume of medium), concentration of dissolved oxygen, the critical elements regarding agitation, and the pressure in the fermenting vessel. Also cite the name and concentration of any antifoaming agents and precursors or inducers of biosynthesis used. The monitoring of antibiotic concentration in the fermentation broth is one of the most critical parameters in the production process. Therefore, the concentration and the method(s) used for its determination should be reported. If a microbiological method is used, the assay microorganism should be indicated, and information should be provided on the sensitivity and reproducibility of the method along with pertinent literature references. In addition, the microbiological and biochemical methods used to control the fermentation process should be described as well as an indication regarding their frequency of use.

Some antibiotic-related considerations concerning extraction and isolation that should be addressed include: (a) the presence of impurities and side products, along with their quantitation and the results of tests assessing their immunologic and toxicologic properties, (b) the development of specific analytical techniques capable of differentiating the product from related antibiotics, and (c) identification of minor active components as well as their levels and respective antimicrobial activities.

e. Drug Substances Isolated from Plant or Animal Sources

For drug substances obtained from plants, the description of their collection and preparation should include the following: (a) botanical species and plant section(s); (b) geographical location(s) where plants with acceptable levels of drug substances are found (the same species can have different levels, when harvested from different locales, because of differences in climate and soil constituents); (c) storage and transportation conditions; (d) drying conditions; (e) grinding procedures; (f) testing procedures to identify and assay crude material, as well as a listing of typical results; and (g) extraction and isolation procedures, where applicable (see also the previous discussion of antibiotics).

The description of drug substances isolated from animal (including human) sources, should contain: (a) species and organ(s) or tissue(s) used, (b) statement(s) demonstrating compliance with USDA or other applicable requirements, and (c) information corresponding to items c–g for plant-derived drug substances described above.

8. *Process Controls*

A brief description of the control checks performed at each stage of the manufacturing process and packaging of the drug substance should be provided. The controls applied to the intermediates should be adequate to assure the correct operation of synthetic and purification procedures, as well as the production of the desired products with the necessary purity. The tests should include identifying the material using at least one physical property (e.g., melting or boiling range, refractive index, optical rotation), detecting impurity/contaminant levels, and monitoring yield. Testing for pivotal and key/critical intermediates should address all of these criteria.

For a pivotal intermediate (one that can be prepared by several different routes), specifications should be rigid and methodologies used should minimize the possibility of the presence of previously undetected or vagrant impurities. The number of steps between the pivotal intermediate and the penultimate intermediate determines the extent of detail and degree of purity required (i.e., the closer they are, the greater the detail and degree of purity required). It should be noted that the pivotal intermediate and the penultimate intermediate can be one and the same.

For a key/critical intermediate (defined as one in which an essential molecular characteristic[s] is first introduced), specifications and test methodologies should be used that assure that the molecular architecture intended to be conferred (e.g., chirality, stereospecificity) has occurred in the expected yield and required purity. At least one test methodology should be used that can quantitate levels of undesired impurities, such as isomers, reaction by-products, or starting materials. For other intermediates, controls may not have to be as extensive. One or more tests monitoring the progress of the synthesis may be all that is necessary.

9. *Reprocessing*

It is expected that operating conditions during the manufacture of the drug substance may occasionally deviate from the synthesis description. If a standard reprocessing procedure has been developed and validated and is expected to be used routinely in the synthesis of the drug substance, include this information in this section.

10. *Reference Standard Preparation*

Describe how the reference standard used to perform the proof-of-structure studies was prepared and how new lots of reference standards will be qualified. If the method of synthesis is the same as that of the drug substance, a statement referencing this fact is sufficient, along with a detailed description of any additional purification procedures performed. These procedures (e.g., recrystallization) should be repeated until important parameters, including assay and levels of impurities, remain unchanged after two successive purification procedures as demonstrated by appropriate tests (e.g., chromatography).

The primary reference standard is normally prepared on a laboratory scale using pure starting materials, reagents, and solvents and should be of the highest purity that reasonably can be obtained. The synthetic procedure used to make it and the method(s) used for its purification, also should be provided. (If applicable, the method of manufacture section can be referenced.) The purification procedure is normally performed until little or no change is observed through two consecutive cycles in assay purity and levels of impurities.

An analytical reference standard or working standard usually derived from a production batch is normally established as the comparative standard for routine analyses of the bulk drug substance for release purposes. It should be characterized against the primary standard.

11. Specifications and Analytical Methods

The regulatory specifications and analytical methods used to assure the identity, potency, quality, and purity of the drug substance should be submitted. The following are examples of attributes that should be monitored:

1. **Appearance/Description.** Color, taste, odor, crystalline form(s), and feel.
2. **Physical Properties.** Melting or boiling range, pH, specific rotation, refractive index, dissolution characteristics in various solvents (including water), and crystallinity (type, such as orthorhombic, cubic, amorphous, and the like).
3. **Specific Identity Tests.** At least one specific identity test that is capable of distinguishing the drug substance from related compounds must be included. Spectrometric tests are usually used, such as ultraviolet, infrared, nuclear magnetic resonance, and mass spectroscopy. Retention times or factors derived from thin-layer, gas-liquid, and HPLC are also used as identification tests to verify a more specific spectral identity test.
4. **Impurity Profile.** Because it requires many hours of work by synthetic and analytical chemists, deficiencies in this area are rather frequent. Impurities should be identified, and at least the major ones should be characterized. Other impurities, when possible, should also be elucidated structurally. Specifications should include limits for each major impurity, as well as a limit for the total level of all impurities. These limits should be based on the known or anticipated toxicologic properties of each impurity, referencing, if necessary, the toxicologic profiles of similar compounds. They also should be based on a review of levels in batches used in longer-term toxicology and clinical studies and demonstrated in these studies to be safe. The reader is referred to the "Guideline for Industry on Impurities in New Drug Substances."

5. **Assay.** The methods for the drug substance and the impurities should be stability indicating. If the identity test is specific and impurities are adequately controlled by other methods, a less specific method to assay the drug substance may be used. If possible, the same procedure should be used to measure both the overall purity of the drug substance and the levels of impurities or degradation products. The limits for purity should be established on the basis of scientific review of the impurity profile of the drug substance and review of results obtained from individual batches.

6. **Other.** Most drug substances used to manufacture dosage forms are solids. It is therefore necessary to consider other properties that may affect the bioavailability with the possibility of eliciting adverse reactions. These parameters, which should be adequately addressed both in the specifications and in the characterization/structure elucidation section, include the nature and extent of solvation, the possibility of different polymorphs, and particle size.

The extent of solvation is routinely monitored by LOD testing conducted at a temperature previously defined by TGA. Either the basis for concluding the existence of only one solvated form or information comparing the respective solubilities, dissolution rates, and physical/chemical stability of the different solvates should be provided.

Polymorphism is customarily monitored by melting point or infrared spectral analysis. However, other methods, such as X-ray diffraction, thermal analytical, and solid-state Raman spectroscopy, also can be used. It is expected that the sponsor will conduct a diligent search by evaluating the drug substance recrystallized from various solvents with different properties. Either the basis for concluding that only one crystalline form exists, or comparative information regarding the respective solubilities, dissolution rates, and physical/chemical stability of each crystalline form should be provided.

Particle size determination may not be important if: (a) the drug substance demonstrates good water solubility; (b) particle size reduction or compaction is performed as part of the dosage form manufacture; or (c) the drug substance is intended to be administered in solution (not suspended). However, the sponsor should be prepared to address with the FDA reviewer why it is not important. The appropriate part of the dosage form manufacturing section, where the data are to be found, should be cross-referenced.

7. **Reference Standard.** Characterization and structure elucidation data are typically derived from tests conducted on the primary reference standard. Its suitability must be documented by information much more extensive than prescribed in the specifications. In addition to the prescribed analyses—especially levels of impurities—other tests normally conducted include elemental analysis and ultraviolet, infrared, nuclear magnetic resonance, and mass spectrometry, along with reviews of each providing assignments of the important features supporting the structure(s) of the drug substance. Other tests such as

optical rotation, refractive index, X-ray crystallography, phase solubility analysis, and differential scanning calorimetry, may be provided as well to support its purity and elucidate its structure. Finally, some compounds may require bioassays for full characterization.

12. Container/Closure System

Provide explicit information regarding the characteristics of, and quality control test methods used by both the manufacturer and the sponsor for, the container, closure, and any other component parts (e.g., desiccant bags) to assure suitability for their intended use. If this information is on file at FDA in the form of a DMF, provide a copy of the letter from the holder of the DMF to FDA authorizing the use of applicable data in conjunction with the review of the sponsor's application. Whenever possible, a similar letter from the fabricator(s) should be obtained and included. In addition, stability data supporting the use of the components should be cross-referenced. Detailed information concerning this subject can be found in the "Guideline for Packaging of Human Drugs and Biologics."

If most of the CMC information drug substance is covered by a DMF, the sponsor needs a letter of authorization to this DMF. The sponsor has to indicate in this section how the drug substance is accepted, maintained, and qualified in its facilities prior to use in the production of the drug product.

Further guidance regarding the required information to be included in support of the manufacture and control sections of the new drug substance can be found in the "Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substance."

IV. DRUG PRODUCT

A. Components

Provide a list of all substances used in producing the finished dosage form intended for commercial distribution, regardless of whether they are ultimately contained in the product. This includes excipients as well as in-process materials, such as water or other solvents used in the granulation process and later removed by drying. The quality specifications or grade (ACS, USP, or NF) should be indicated for each substance.

If proprietary mixtures (colorants, coating mixtures, flavors, controlled release matrices, imprinting inks) are used as components, information on their compositions should be provided. Any alternates that have been evaluated and determined to be interchangeable also may be included. The sponsor should be prepared either to delete the alternative from the application or to generate further information, including effects in the bioequivalency, in support of retaining the alternative if FDA initially does not accept it.

B. Composition

The statement of composition for each active or inactive ingredient per unit of dosage form (e.g., tablet, capsule, ml) should be provided. In addition, include a batch formula that is representative of the scale of manufacture to be used. Besides the name, strength, and type of dosage form, the name and weight of each active ingredient and the identification of all components should be given. This should include their grades in the same manner as defined under Components. Information to be included will usually consist of the weights and measures of each component using the same weight system, any calculated excesses, and the theoretical weight and number of doses to be obtained. Reasonable variations in the amounts of inactive components (e.g., +10%) are usually permitted and are generally indicated on the quantitative composition. Dosage forms, however, must be formulated to contain 100% of the desired potency. Whereas the allowable range for the potency of a drug might be 90% to 110% of its labeled potency during its labeled shelf-life period, a sponsor cannot change the formulation to achieve 95% of the labeled potency in an effort to reduce the cost of manufacturing.

C. Specifications and Analytical Methods for Inactive Components

Inactive components are sometimes referred to as inactive ingredients, ingredients, or excipients. These are all the items in the listing of components used to manufacture the drug product except the drug substance(s). If an inactive component is USP/NF grade, it is acceptable to just reference the current monograph for that component. If the inactive ingredient is non-USP/NF but belongs to a foreign compendium, provide a copy of the actual monograph for this inactive component. The FDA will at times accept the specifications and test methods indicated in the foreign compendium but can ask for validation data for the assay method. Acceptable food or color additives are indicated in the 21 CFR, and batch certifications are needed for some of the color additives before they can be released for production. A batch certificate for the NDA batch should be included.

Indicate which tests will be performed routinely by the sponsor on each lot received. Most sponsors will perform all tests specified in the monograph for the first few batches until comparative data are achieved with the manufacturer's Certificate of Analysis; then they rely on Certificates of Analysis and perform an identity test for each batch.

In the case of noncompendial materials, specifications and complete descriptions of the test methodologies to be used for quality control release purposes by the sponsor should be included. In addition, it may be necessary for the sponsor to obtain a letter authorizing reference to a DMF from the supplier concerning the manufacturing and controls procedures used to make these materials, such as mixtures of colorants or flavors. It may be necessary to obtain toxicity data if the mixture or component has little or no history of human use (e.g., new polymers). If it is anticipated that an "untried" component will be used, it is recommended that discussions be initiated with the FDA's reviewing chemist and pharmacologist. These sessions should be scheduled as soon as possible to minimize the possibility of delays in NDA approval caused by inadequate information to support use of the material.

D. Manufacturer

The names(s) and address(es) of all manufacturers, contract packagers, and contract analytical laboratories used for testing raw materials or the drug product should be given. If the manufacturing site is in the United States, a general description of site facilities and operations should be incorporated because information on these facilities is available in the FDA District Offices. If the manufacturing site is in a foreign country, letters authorizing FDA reference to site DMFs (type I) on behalf of the sponsor should be included. If a DMF is not available, then information that is needed to prepare a type I DMF should be obtained by the sponsor from the manufacturer. This information is then placed in this section. Refer to the "Guideline for Drug Master Files."

E. Method of Manufacture, Packaging Procedure, and In-Process Control

In this section, include a general description of the manufacturing procedure, including all processing alternatives previously validated as producing acceptable product. The FDA also wants copies of the proposed or actual master production and control record, as well as a copy of a completed production and control record for a typical batch. It is also helpful to provide a schematic diagram for the flow of materials, the production process, and an indication of the equipment to be used.

For other than manual operations (e.g., computerized automated plants), the schematics are more critical to assure that the FDA reviewer understands the process. The description should also indicate the various points of sampling.

The piece(s) of equipment that renders the batch homogeneous before packaging should be identified, with both the useful working and total capacities noted.

Regarding reprocessing operations, adequate information should be submitted to permit approval of such procedures, for bulk, in-process, or finished drug products that do not conform to established specifications. The original application may include proposals for such steps that cover foreseeable deviations, such as unacceptable weight variation, content uniformity, and tablet coating. Deviations not covered in the original application should be covered by a supplemental application and must receive approval before commercial distribution of such reprocessed product. All proposals should include a description of the material that includes a statement of the deviations(s), a detailed description of the reprocessing procedure, including additional controls to be used over and above those established for routine production, and information on the maximum allowable time between initial manufacture and initiation of reprocessing operations, along with the applicable storage conditions to be used during this interval.

A sample packaging record(s) that describes the packaging and label operations also should be included with the manufacturing and control record and the completed production and control record for a typical batch.

1. *Regulatory Specifications and Analytical Methods for Drug Product*

Consistency in the quality of the drug product batches is controlled by the specifications and analytical methods set for that product. This means that when the drug is taken by a patient, the expected clinical response will occur. Specifications and analytical methods evolve throughout the investigational phases of drug development. By NDA time, a sponsor has learned much about the nature of the drug product and the critical parameters that have to be monitored to provide maximum assurance of its safety and efficacy. It is at this point that the regulatory specifications and analytical methods are determined for the drug product. These are established to assure the safety and efficacy of every batch of drug product up to the date of its expiration. The NDA also should include appropriate information on in-process controls and a listing of the number or amount of drug product needed to perform each of the regulatory analytical methods.

Regulatory specifications may differ from product release specifications. Regulatory specifications assure acceptable product potency until the labeled expiration date or shelf-life. In general, in-house release specifications are tighter than regulatory specifications.

Refer to the "Guideline for Submission of Supportive Analytical Data for Methods Validation in the New Drug Application."

The following items should also be considered.

a. Tablets, Capsules, and Other Dosage Forms

1. Weight variation.

2. Content uniformity for tablets, capsules, sterile solids, and sterile suspensions. A common deficiency is the use of different analytical methodologies for uniformity and for assay purposes without supporting their equivalency or adequately defining correction factors.

3. Dissolution rate tests for tablets, capsules, suspensions, suppositories, or other dosage forms. Controlled-release dosage forms or drug delivery systems also should be monitored by appropriate testing methodology.

4. Moisture content. In some formulations of relatively water-insoluble drug substances containing anhydrous lactose, storage under high humidity conditions (75% or higher) has been shown to adversely affect dissolution rates.

5. Loss on drying, where applicable.

6. Physical characteristics such as color, appearance, odor, shape, hardness, thickness, friability, and coating. Fading and brittleness (powdering) are common problems.

7. Softening or melting points and particle size distribution of suspended drug (suppositories).

8. Assay(s) for the active drug substance in the drug product, for impurities, and for degradation products.

b. Solutions and Suspensions

1. Clarity, limit for the presence of particulate matter, preservative effectiveness, and assay, isotonicity (ophthalmics and injectables), and pH
2. Sterility of ophthalmics
3. Sterility, apyrogenicity, and container fill of injectables
4. Leakage test for ampules, vials, sachets, aerosols, strips, tubes, and so forth
5. Spray pattern and container pressure for aerosol products; for a metered dose product, reproducibility of actuated dose and defined limits for dose administered per actuation
6. Particle size specifications for the active component; resuspendability, viscosity, sedimentations rates, caking, and syringeability of suspensions
7. Completeness and clarity of constituted solutions

c. Plastic Devices Containing Active Drugs

1. In vitro rates and identity testing of all plastic components. If applicable, determine sterility and measure levels of residual ethylene oxide and its decomposition products.

2. Additional physical tests, such as frame memory, resiliency, tensile strength, and seal integrity.

d. Diluent Solution

1. Full specifications and analytical methods, including preservative levels.

2. Container/Closure System(s)

Describe all the packaging configurations to be used for the drug product. List the components that comprise each container/closure system to be used.

Provide a detailed description of the physical, chemical, and if applicable, biological characteristics of the container, closure, or other component parts of the drug product package to assure suitability for its intended use. Acceptance specifications and test methods performed by the drug product manufacturer for each packaging component should be spelled out.

The "Guideline for Packaging of Human Drugs and Biologics" includes specific recommendations for the format and content of this section. Some points need to be emphasized, however, to help the sponsor avoid delays in NDA approval because of deficiencies in container/closure information.

When more than one plastic resin is used to fabricate bottles, it is necessary to demonstrate the equivalency of the container produced using the different resins. In addition, comparative data derived from light transmission, chemical resistance, extractables, and moisture permeation/vapor transmission tests described in the USP should be provided as applicable to the type of product. (For example, moisture permeation for an aqueous dosage form would not be necessary). Whereas the compendia discuss these tests only in the context of polyethylene, the guideline makes no distinction as to the resin used. It also should be verified that copies of letters authorizing FDA reference to appropriate DMFs from manufacturers of the resins used to fabricate bottles and from the bottle fabricator(s), if available, are included. Although most resin suppliers include information on extractables data in their DMFs, it should be pointed out that fabricators may have to add release agents or other additives not covered by extractables data in the DMF of the resin supplier.

Manufacturers of glass components, in most cases, do not have DMFs. It is recommended that letters be obtained from fabricators certifying that the glass used will meet appropriate compendial requirements (i.e., US type I or type II glass).

For closures, compatibility of the drug product with the inner liner/contact surface should be evaluated. This is usually done as part of stability studies conducted on a product stored inverted. If available, appropriate DMF authorization letters should be obtained to support suitability of the closure and liner

Provide information on any adhesives used for blistered packages. Defect classification data should be considered. Permeation and leaching/migration testing should be conducted and reported. (Information in a DMF or data from studies conducted by the fabricator may be sufficient.)

For elastomers (e.g., stoppers), leaching of components is a concern, as is the possibility that components, especially active drug substance from the formulation, will migrate into the closure. Therefore, test data should be provided that demonstrate drug product/closure compatibility. A letter from the closure manufacturer authorizing FDA reference to their DMF should be obtained and included.

Finally, for any unusual or uncommon containers and closures, sufficient information about the materials of fabrication, design performance, and other information that conclusively demonstrates their suitability for use with dosage form should be provided.

F. Stability

This section, as previously discussed, frequently poses problems leading to delays in NDA approval. Particular attention should be paid to the development of adequate data from studies conducted with commercial formulations packaged in container/closure system(s) to be marketed. It is critical that adequately validated analytical methods be used as early as possible in the investigational phases of drug development—no later than the initiation of phase 3 studies. Common defects in stability studies submitted to FDA reflect the lack of acceptable long-term or short-term accelerated stability data to support the approval of an expiration date for the product. Another common problem occurs when studies are conducted using only one container size, yet the sponsor is applying to market two or more sizes. As a general rule, FDA wishes to see data from studies conducted on at least the smallest and largest sizes to be marketed (e.g., 100- and 500-tablet bottles or 2- and 32-ounce bottles). Blister packs are generally exceptions to the rule because each dosage unit is individually packaged.

With drug products containing preservatives, the stability protocol should include preservative efficacy testing. Microbial challenge testing should be conducted at appropriate intervals—at least once a year unless significant losses are observed earlier as a result of assay procedures.

Other items worth considering in the design of a stability protocol are the effects of heat, humidity, freezing (for solutions, emulsions, and semisolids), and light. These data are needed to support the recommended storage conditions required to be on the product labeling. The information also helps answer the inevitable questions from the field (e.g., the product has been stored in a warehouse whose air conditioning unit broke, and the customer wants to know if the product is still good after storage for a month at 110° F). Simulated use tests are also recommended, in which the same bottles are opened and closed a number of times and the data are compared with the stability of drugs stored in unopened containers.

For products intended to be reconstituted, it is necessary to conduct stability studies on the final product form to determine the maximum allowable storage time after reconstitution. Data from these studies, usually conducted over a period of a week or less, support recommendations required to be on the labeling for storage time and conditions after reconstitution (e.g., "Administer within 3 hours after reconstitution. Store until use under refrigeration [2° to 8° C or 35° to 45° F.]"). If previous studies have demonstrated light or heat sensitivity, these conditions should be considered in designing studies of the reconstituted product.

In addition to potency, other design considerations that may need to be incorporated in the stability protocol for various dosage forms include the following:

Tablets: Appearance, friability, hardness, color, odor, moisture, and special emphasis on dissolution rates.

Capsules: Moisture, color, appearance, shape, brittleness, and especially dissolution rates.

Emulsions: Appearance (particularly with regard to phase separation and color), odor, pH, viscosity, and the effects of heating and cooling.

Oral Solutions and Suspensions: Appearance (clarity, the presence of a precipitate, cloudiness), pH, color, odor, redispersibility (suspensions), and storage both in upright and inverted positions to determine if the closure or liner adversely affect stability.

Oral Powders: Appearance, color, odor, moisture content of powder, and, if intended for reconstitution, appearance, pH, and dispersibility/dissolution properties.

Metered-Dose Inhalation Aerosols: Quantity of delivered dose, total number of acceptable doses delivered, color, solvate formation with propellant, particle size distribution, weight loss of canister (i.e., loss of propellant), pressure, valve corrosion, and storage in both upright and inverted positions.

Topical and Ophthalmic Preparations: Appearance (clarity, color, and especially homogeneity), odor, pH, resuspendability, consistency, particle size, weight loss (of more importance if plastic containers are used). Sterility and preservative levels also must be considered if the product is intended for ophthalmic administration.

Small Volume Parenterals (SVP): Appearance, color, clarity (particulates), pH, and sterility checks at reasonable intervals are minimum standards. Powders for reconstitution should also include residual moisture and stability checks after reconstitution. Except for ampules, upright and inverted storage of final product should also be evaluated.

Large Volume Parenterals (LVP): Similar evaluations as described for SVPs should be conducted. In addition, if plastic containers are used, volume and extractables data should be evaluated. Another important parameter to consider, if applicable, is the maintenance of adequate preservative levels over the expiration dating period.

Suppositories: Appearance, melting range, dissolution at 37° C, body temperature, and aging with respect to hardening and polymorphic transformation.

Drug Additive: Compatibility of admixture, appearance over 24 hours including evaluations of both drug and additive for assay, pH, color and clarity, and interaction with the container at the time of mixing (time 0) and 2–3, 6–8, 12, 24, and 48 hours after mixing. Some intervals may be deleted or the time intervals adjusted as considered appropriate or cost effective.

Statistical Analyses: The statistical analyses of data submitted to support a proposed expiration date should be described fully. In addition, as part of the stability protocol, provide detailed plans for such analyses of future batches.

Stability Reports: These reports are frequently deemed incomplete because adequate information for each lot of product are missing. Data must be provided describing formulation; batch number; scale of manufacture including designation as to whether a laboratory, pilot, or production lot; site(s) of manufacture; and the analytical methodology(ies) used, reflecting changes, if any, made during the course of the investigation. Notations regarding the status of each lot (whether it is terminated or continuing on stability) should also appear on each table of data.

Stability Protocol: A postapproval stability protocol should be submitted documenting future plans. It should include information on time points and storage conditions to be evaluated, and indicate whether extensions of expiration dating are intended based on sponsor evaluation of data obtained following the protocol. These data will still have to be submitted, as well as the details of the extensions of expiration dating being implemented, in the annual reports filed with FDA. Also indicate how many batches of drug product will be placed on stability in a year.

G. Environmental Assessment

The format and content of this section for NDAs and ANDAs can be found under 21 CFR 25 Subpart C. In addition, FDA generated a guidance document that provides a more in-depth description and clarification of items to include in this section. This document is entitled "Guidance for Industry on the Environmental Assessment in Human Drug and Biologics Applications, July, 1998."

V. SAMPLES

Identify all samples being set aside for FDA validation. The samples should include drug substance, drug product, major impurities, and degradation products being controlled for, references standard, and internal standard (the latter is not required if commercially available but is recommended to facilitate FDA laboratory work). If appropriate, blanks and any other materials not commercially available but specified in the analytical procedures should be provided. The samples are to be maintained by the sponsor until the FDA's reviewing chemist provides instructions as to where they should be forwarded. The total quantities and the manner of their subdivision (e.g., 400 tablets, 4 × 100 tablets/bottle) should be indicated. The amounts provided should be adequate to permit at least three separate determinations, excluding sterility, by two different laboratories.

VI. METHODS VALIDATION PACKAGE

Unlike the full NDA, which is submitted in duplicate, this section must be provided in triplicate because copies are forwarded to two FDA laboratories. These laboratories will assess the validation data and test the drug substance and drug product to verify the validity of the regulatory specifications and test methods indicated in the NDA. Documents in this package that were taken from the CMC section should retain the original pagination in the CMC section. Intended to expedite the NDA review and FDA laboratory validation of proposed regulatory methods, it is recommended that the submission include the following items.

A. Test Methods and Specifications

Copies of regulatory specifications and analytical methods for the drug substance and drug product should be provided. These documents should retain the original pagination they had in the CMC section.

B. Supporting Data

Validation information to support the suitability of the regulatory analytical method(s) is shown by providing data on accuracy, specificity, sensitivity, precision, ruggedness, and linearity over the range of interest. The emphasis for analyzing drug substances is the control of the presence of impurities. With drug products, it is more important to quantify the active drug substance and level of degradation products throughout the expected shelf-life of the product. (Levels of impurities that are not degradation products are adequately controlled in the bulk drug substance-release testing.)

Documentation (or lack thereof) provided in support of specificity, sensitivity, and ruggedness are frequent sources of FDA comment and delays in NDA approval.

Specificity: It is not advisable to rely on drug substance assay results (and assay specificity demonstrated only with respect to impurities) on the assumption that degradation products behave similarly. Specific studies to determine degradation pathways must be conducted. These should include exposing the drug substance to acid(s), base(s), heat, light, oxidizers, reductants, and combinations of the above, as appropriate. It the absence of suitably designed degradation studies, it is not possible to know the intrinsic stability of the drug substance, or to determine in future studies whether any given peak on a chromatogram is an artifact or a real degradation product. It also may be difficult to establish whether the chromatogram is run long enough to permit the observation of peaks from degradation products. In addition, excipients in the dosage form may interfere with one or more peaks of interest. The specificity of the method(s) should be evaluated by treating the formulation minus the active ingredient(s) in similar fashion to the dosage form before injecting or spotting. It is strongly recommended that the methods include retention information for all degradation products known or still in the process of being identified to facilitate their monitoring by different analytical chemists during the course of the stability studies.

Sensitivity: This can be a source of FDA comment, when information is not included in the validation documentation on the sensitivity(ies) of the method(s) to detect and quantitate the drug substance and the degradation products. In addition, the methodology description should include the appropriate mathematical formula(e) to be used for calculating their respective levels. Even if the sponsor uses a computerized system that provides the number directly, these formulae should still be provided to facilitate manual calculations.

Ruggedness: This is also an important consideration, because it is directly linked with the probability of success for the FDA laboratories validating the methods internally (i.e., analyst-to-analyst, lab-to-lab reproducibility results). It is recommended that the sponsor have a second laboratory perform the method using a different instrument and column, if possible. By following this recommendation, potential misunderstandings regarding the performance of the various operations and manipulations can be identified and rewritten for clarity to facilitate use of the selected method. In addition, in the case of chromatographic systems (HPLC or GC), the appropriate peaks and their minimum resolution (separation) factor can be determined and noted in the method of description as the parameters to be monitored by the analyst to assess the suitability and effectiveness of the operating system before conducting the assay. This assessment should be performed routinely and is commonly referred to as "system suitability testing."

Other Areas: Those that can lead to approval delays include the following: (a) use of instrumentation not commercially available and the absence of a detailed description of the components and assembly, (b) use of single source specifications to permit duplication, (c) use of specialized tools or equipment not available to the FDA chemists for sample preparation, (d) use of an inhouse standard or other noncommercial reagent, and (e) failure to provide a system suitability test on chromatographic procedures.

Data from these and similar sources should not be submitted unless it can be demonstrated that no acceptable alternatives are available.

Include documentation supporting the integrity of the reference standard.

For additional information, the reader is directed to the "Guideline for Stability Studies for Human Drugs and Biologics," and the "Guideline for Submission of Supportive Analytical Data for Method Validation in New Drug Applications."

C. Test Results

Provide the certificates of analysis for drug substance, drug product, and reference standard for the lots where the samples were obtained.

In support of samples of impurities, degradation products, and internal standards, it is recommended that copies of relevant spectra and other supportive analyses used to elucidate or verify their structures be included.

VII. ABBREVIATED NEW DRUG APPLICATION

There are distinct differences and some unique problems likely to be encountered in the preparation of manufacturing and controls sections for ANDA submissions. Some of them are highlighted below.

A. Summary

A summary is not required by the FDA. Its preparation, however, might help the sponsor pinpoint potential deficiencies. If the application is among the first being submitted for a drug whose patent is about to expire, the summary may help the FDA's reviewing chemist become familiar with the drug.

In lieu of a summary, information should be provided that shows the proposed product is the same as a listed product (eligible products are listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations") with respect to its indications for use, active ingredients, route of administration, dosage form, strength, bioavailability, and labeling. Patent certification information and any indications for which the ANDA sponsor is not eligible because they were exclusively approved to a previous NDA sponsor should also be provided.

B. Drug Substance Sources

Drug substances that are used in the manufacture of drug products that are the subject of ANDAs are usually obtained from one or more external manufacturers, frequently located overseas, and imported into the United States. Under FOI it is important to obtain a copy of a potential supplier's most recent EIR describing FDAs findings. This document should be reviewed by the sponsor to assess the likelihood of the supplier's acceptability to FDA as a manufacturer. In addition, the supplier should have a DMF available at FDA for reference purposes. This will describe the facilities, personnel, equipment, and manufacturing and controls procedures used at the site(s) where the bulk drug substance is made. The ANDA sponsor can then submit a much simplified drug substance section because the letter of reference to the DMF serves in place of providing specific details regarding the manufacturing procedures, controls, stability data, and identification of impurities. These and other relevant issues should be assessed by direct discussion with the manufacturer and, if necessary, arrange to have the manufacturer update the DMF.

C. Specifications

This subject is usually not a problem, if compendial (USP) monographs exist. Analytical methodology, however, can be a troublesome item. This is especially true with older drugs where assay methodology specified in the monograph is not sufficiently specific and in the case of drugs for which there are no published compendial monographs. An FOI request to FDA for a copy of the pertinent regulatory assay method will prove helpful in minimizing the amount of analytical development work to be carried out.

It is prudent to evaluate impurity peaks observed in a supplier's bulk substance and compare them with those observed in the drug product. The extent that the peaks differ may determine the need to obtain further information, including toxicity. Samples of impurities/degradation products methods should be appropriately validated by the ANDA sponsor for their sensitivities and specificities. It also is recommended that the sponsor of an ANDA set up and maintain a stability program for the bulk drug substance.

D. Drug Product Requirements

Drug product requirements are similar to those described previously for the NDA. The extent of stability data submitted, however, is much less than that usually available for an NDA. Specifications are usually defined by a published compendial monograph. It must be emphasized that analytical methodologies for many older drugs, as set forth in their monographs, may not be sufficiently specific to be accepted by FDA as "stability-indicating." It is also possible that the drug product may not have a published monograph. A request should be made under FOI to obtain a copy of the regulatory assay method. Adequate validation studies should be carried out to verify the accuracy, precision, specificity, recovery, and sensitivity of the method(s) conducted by the sponsor's own laboratory or contact facility. It is also important to compare the release characteristics of the sponsor's product with those obtained with the original brand name product using the same methodology. For example, data comparing the dissolution characteristics and performance of the sponsor's and the brand name tablet or capsule products at several different time points (as applicable to obtain 95% or more of drug in solution)—otherwise referred to as a comparative dissolution profiling—should be obtained.

E. ANDA Expiration Dates

Generally, the FDA will tentatively approve a 2-year expiration date for a product if satisfactory data reflecting at least 3 months' storage under accelerated conditions is submitted. The sponsor is also expected to provide a commitment to continue to monitor the stability of the product, periodically report the results to FDA, and to remove from the market any batches failing to meet specifications prior to the product's labeled expiration period. Final approval for the expiration date is obtained when acceptable shelf-life data for 2 years or more than one production lot is made available to FDA. In contrast to NDAs for which the extended term data are frequently available prior to approval, the importance of the stability protocol describing future plans, including the basis that the sponsor deems appropriate to support an extension of a product's expiration dating, is magnified for an ANDA. In fact, an ANDA will most likely not be approved without the inclusion of a suitable stability protocol.

The FDA generated a guidance document regarding the content and format of an ANDA entitled "Guidance for Industry: Organization of an Abbreviated New Drug Application and an Abbreviated Antibiotic Application (February, 1999)."

VIII. CONCLUSION

In the context of the guidance documents issued by the FDA, this chapter has explored the various issues, and described a number of recommendations, concerning the documentation requirements for NDA and ANDA submissions. It is anticipated that as industry representatives become more familiar with these guidance documents, the quality of CMC documentation will be improved, and it is hoped that the frequency and extent of deficiencies will diminish. One of the most positive contributions will be the economical one, because reproducible manufacture of new drugs in well-designed dosage forms can be prescribed by physicians with confidence. The careful preparation of the manufacturing and controls section in an NDA or ANDA can facilitate FDA processing, review, and approval procedures. The result is potentially faster commercialization of new products benefiting both pharmaceutical manufacturers and the patients they ultimately serve.

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8

Clinical Research Protocols

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I. INTRODUCTION

The practice of clinical research—to establish safety and efficacy for new drugs, devices, and biologics—is considered the most important part of the new drug approval process by many individuals in the FDA, sponsor companies, and users of pharmaceutical products. Accomplishing this task requires careful strategic planning to meet research objectives, an available patient population that meets the criteria of study requirements, and experienced clinical investigators who can evaluate the study subjects according to the protocol design.

Clinical research protocols are the key to assuring successful approvals of new products in the health care industry. The protocol becomes the Bible for each research program. It must be followed exactly, without deviations, and must be the reference for any discussions that arise during the course of the investigation. This chapter will give instructions on how to write a clinical protocol for all phases of clinical research. It will include all necessary FDA requirements for confirming safety and efficacy for products marketed for human use. The format for protocol development is recommended on the basis of its successful use in clinical research. The recommendations throughout this chapter may not always be applicable to all clinical programs.

The objective of most clinical studies is to record scientific data concerning the efficacy and safety of a treatment for a specific disease on which valild conclusions can be drawn. The degree of success in achieving this objective depends largely, but not entirely, on the quality of the basic study design. Faulty execution, due either to sloppiness or (in rare instances) dishonesty, can undermine the validity and usefulness of the data generated from a particular study site. All investigators and their staffs must be meticulous in observing and reporting their clinical observations. On the other hand, even if a lengthy study is carried out with the utmost care, the data generated will be useless if the protocol has not been designed intelligently. Overall, it must include all the necessary ingredients so that the eventual clinical results will support IND and NDA submissions.

Because the framework of every clinical research study relies on a number of interdependent disciplines, the development of a clinical study protocol is ideally a multidisciplinary task. Teamwork, coordinated by one experienced person in clinical research with good knowledge of the regulatory requirements for new drug development, is essential. The protocol design team should also include input, recommendations, and review by the following:

A chemist who is fully conversant with the physical and chemical properties of the investigational drug

A pharmacologist and/or toxicologist with a full understanding of the pharmacology and toxicology of the drug in animals and the expected effective dose, therapeutic effects, and possible side effects in humans

A medical monitor, preferably one who specializes in the condition or illness to be studied, and who is experienced in the logistics and practicalities of clinical trials

A statistician who will address those aspects of study design that determine the form the study data will take for analysis and the types of analyses that will be applied to the data

A data management person who will be both involved in coding and in charge of data entry

A potential investigator or consultant who understands the indication to be researched and the objectives of the protocol and procedures to be followed

A capable program manager who can coordinate the multidisciplinary effort to form a final protocol and affect practical execution in the clinical setting straight through to data analysis and final write-up

Together, these specialists can provide both the criteria for all aspects of the study and the rationale used to develop them. Once the specific objectives of the protocol have been established, it is customary for a protocol introduction to summarize these objectives, give a brief overview of the information found in the Investigator's Brochure (referencing the Brochure), and state the purpose of conducting the study. The rationale for the criteria to be used for patient selection, exclusion, and randomization (if any) and the clinical variables to be monitored during the trial should also be stated.

II. STUDY OBJECTIVE

A common fault in study design is to have too many objectives in a single study. Objective(s) should be clearly and concisely stated. If a study has more than one objective, the objectives should be listed in order of priority. The fewer the questions to be answered in one study, the greater the likelihood that they will be answered conclusively. The key to successful study design is simplicity.

III. GENERAL CONSIDERATIONS IN PROTOCOL DESIGN

The study protocol is the end point of research design. It is the blueprint that displays the elements of the study plan and provides explicit instructions as to how the plan should be executed.

The protocol designers should approach the subject by first organizing a checklist similar to the one presented later in this chapter (see Elements of a Protocol: A Checklist). This list will serve in protocol design much as an outline helps a writer or a speaker touch on all salient points in an article or speech. Judging from the number of NDAs that are returned to their sponsors for more clinical information (time-consuming revisions) by the FDA, one might assume that there are tricks to the art of a successful filing. No secret ingredients are needed for the successful preparation of a clinical protocol or its presentation within an IND and ultimately the NDA—just logic, completeness, and a practical understanding of the disease under investigation.

In drug development, time is of the essence. Clinical protocols should be concise, straightforward, and logical. The demands upon the investigators, their staffs, and the patients must be reasonable. The FDA's guidelines for drug development by disease must be considered in order to expedite the final NDA review and approval. The objective to remember throughout protocol development, and execution and presentation of the acquired data, is to demonstrate efficacy and safety to fulfill FDA's requirements for NDA approval.

IV. DIFFERENT STUDY DESIGNS

Conventionally, phase 1, 2, 3, 3b, and 4 studies refer to the successive stages of the clinical investigation of a drug or the continued experiment of the same. Although the objectives of all of the phases are different, they are not entirely separate entities because the information obtained from one phase provides the basis for the next. In broad terms, the objective of phase 1 is a demonstration of safety based on dose tolerance; phase 2 is for dose tolerance and safety balanced with efficacy (probably the most important phase in clinical research development); phase 3 reconfirms efficacy and safety in a larger patient population for a specified dose and indication in the intended patient population; phase 3b is designed for large-scale safety. Phase 4 studies are usually classified as marketing studies and are designed to demonstrate how similar drugs, prescribed for the same indications, may show one having certain advantages over another. The basic principles of good scientific methods of study design apply equally to all five phases. The major tenets of all scientific experimentation should be regarded as fundamentals of the design: the possibility of coincidence as well as bias should be ruled out, and the results produced by the study design should be as conclusive as possible. In other words, the study should be controlled, designed, and analyzed for optimum statistical reliability and specificity.

V. CONTROLLED STUDIES

A study drug can be compared with a placebo or with an active drug. If active medication is used as a control group, it should be a standard drug accepted in medical practice for the specific indication(s) under investigation. Double-blind trials are usually indicated to best assure that the data obtained from these studies, when evaluated statistically, will support judgments regarding the safety and the efficacy of the investigational drug without bias. Because of ethical considerations, however, there are many drugs that cannot be evaluated under double-blind conditions. In these cases, a sponsor should review the situation with FDA and establish the acceptability of data to be obtained from a trial of alternate design before the study has begun. It is not unusual, however, for phase 1 studies to be open-label (not blinded), because the objective is to observe the response to the investigational substance primarily in terms of safety.

Double-blinded, controlled studies that are well designed yield the most valid results. In the majority of investigations, test agents are blinded against placebo controls. The FDA's NDA approvals, in most cases, are based on the following: two clinical studies proving that a drug versus placebo shows statistically significant difference. These are termed pivotal studies. Rare exceptions are made, with active agents used as controls assumed to exert similar therapeutic conditions.

Very rigid criteria are established to preclude investigator or patient bias. Impressions of drug efficacy or lack of the same based on previous evaluations of reported efficacy must be avoided.

In a study comparing the effects of two or more treatments, if the investigator or the patients are aware of the treatments administered, the preconceptions and prejudices of both toward the treatments can have a significant biasing influence on the accuracy with which assessments of the effects of the treatments are made. This extraneous variable of bias can be minimized by suitable blinding techniques. The single-blind method, as the name implies, ensures that only the patient is unaware of the distribution of treatments during the study. The double-blind method, which is now accepted as the standard blinding procedure in comparative drug studies, ensures that both the investigators, their staffs, and the patient are unaware of the type of treatments that are being prescribed and administered.

A. Blinding Techniques

Attaining and maintaining double-blind conditions in a clinical study requires strict attention to a number of details. A drug form identical to the test drug is necessary for double-blind conditions. Pharmaceutical manufacturers can usually supply their products, placebo, and comparison drugs in forms that meet these requirements. Comparative evaluation studies cannot be done on drugs in dissimilar formulations, such as tablets versus syrups, ampules versus suppositories, or liquid concentrates versus capsules. Additional blinding problems are presented by variations in physical characteristics including color, taste, texture, viscosity, shape, or size. If a study calls for the comparison of two treatments with formulations that make physical matching impossible, the problem can be solved by the double-placebo (double-dummy) method, which establishes manifest equality of product characteristics. It consists of simultaneously administering to each patient an active test agent and a placebo of the other active agent that is being evaluated (Table 1).

Inasmuch as the two agents (whatever their forms) are administered simultaneously to each patient at all times during the trial, there is no way of telling the difference between active drug and placebo. In all cases, the assigned placebo is physically identical to the test agent and is administered through an identical route. In addition, the method can be adapted to compare a suppository with a liquid concentrate or a syrup with a capsule. Any two drugs with different routes of administration, or different forms, can be effectively blinded in this manner and can satisfy all the rigid requirements of classical, double-blind, clinical research studies.

Table 1 Double-Placebo Method

Group 1 Patients	Group 2 Patients
Active Drug A tablets	Active Drug B liquid
+	+
Placebo B liquid	Placebo A tablets

The procedure also can accommodate the double-blind evaluation of two active agents that must be administered at different times of the day because of their dissimilar modes of actions. Table 2 demonstrates how all patients receive an active agent and placebo or two placebos at the same time.

Active drug and placebo are administered twice a day to all patients in both groups: 4:00 PM and 8:00 PM for group 1 patients; and 7:30 AM and 4:00 PM for group 2 patients. During each day, patients in both groups receive a total of two doses of drug A or drug B, but at different times of the day.

Table 2 Delivery of Two Active Agents with Different Administration Regimens

Time of Administration	Group 1 Patients Drug A (tablets)	Group 2 Patients Drug B (capsules)
7:30 AM	Drug A Placebo + Drug B Placebo	Drug A Placebo + Drug B Active
4:00 PM	Drug A Active + Drug B Placebo	Drug A Placebo + Drug B Active
8:00 PM	Drug A Active + Drug B Placebo	Drug A Placebo + Drug B Placebo

The double-placebo method can help overcome the problem of blinding drugs that are dissimilar with regard to color, taste, viscosity, volume, dosage equivalency, or dosage regimen. It can only prove successful under good clinical management conditions and meticulous monitoring of the study to assure full compliance. Double-blind, double-placebo techniques depend on reliable research coordinators who consistently check on drug administration and accountability, and in turn, close monitoring is required.

No matter how rigorous the enforcement of blinding techniques, circumstances may arise that threaten the integrity of the blindness of a clinical study. For example, a larger number of adverse reactions in one treatment group compared with another may provide a clue as to which treatment is involved, particularly in placebo-controlled studies. Likewise, different patterns of symptom response in treatment groups may suggest the treatment involved.

Blindness can also be destroyed by accidental breaking of the randomization code. With good design and adequate safeguards, however, this should not occur.

The only circumstance under which the identity of study materials should be deliberately known is when a patient has an adverse reaction that makes it imperative for the investigator to know which treatment the patient received.

However, the method of labeling the study drugs should allow for this to be done without revealing the randomization code for the entire study. One such technique is for each medication container to have a two-part label, one of which is a sealed, tear-off section containing the identity of the drug. At the time the patient begins treatment, the tear-off section is detached and affixed to the patient's case report form and can be opened in an emergency.

VI. UNCONTROLLED STUDIES

Most regulatory bodies, concerned with the approval of new drugs for clinical use, do not accept the results of uncontrolled studies as stand-alone evidence of efficacy. There are, however, circumstances under which data from uncontrolled studies can provide acceptable evidence of efficacy: (a) the treatment results in consistent and clinically significant improvement in a disease with a well-established natural course and remission rate, (b) the treatment consistently results in significant improvement in all or almost all patients.

Apart from the limited value of uncontrolled studies for the demonstration of efficacy, they may be helpful in obtaining an early indication of the optimum dose, the adverse reaction potential, and the preferred route of administration of a drug. As a general rule, it is best to confine clinical drug studies in phases 1, 2, 3, and 4 to those that use adequate controls and unbiased techniques.

VII. PARALLEL AND CROSSOVER STUDY DESIGNS

Controlled trials can be conducted under matched pairs, parallel, crossover, group comparisons, or mixed design conditions. Parallel and crossover study designs each have advantages and disadvantages. Both can be used to compare two or more treatments, one of which may be placebo. In a crossover study, all treatments to be compared are administered to every enrolled patient in a carefully designed and blinded sequence with an interim drug washout period. Each patient receives all treatments and thus serves as his or her own control.

In a study using parallel groups, patients are randomly assigned to one of the treatments (which might be placebo). In spite of adequate selection criteria and random assignment, the treatment groups in a parallel group study may indeed differ. Fewer patients are required in a crossover study than in a parallel group study. Although the desired duration of exposure to each treatment can be achieved, patients have to participate in a crossover study for at least twice as long as in a parallel group study. This makes it especially necessary that the clinicians selected have good rapport with the patients, therefore demonstrating the ability to maintain a low patient attrition rate, as well as protocol compliance. In addition to this potential source of difficulty, another drawback of the crossover method should be noted: if two active drugs are being compared, all patients are exposed to the possible safety hazards of both drugs, or in the case of a placebo, the risk of allowing the pathology to go untreated. For the results of a crossover study to be valid, each patient must be in the same clinical condition at the beginning of the second treatment period as at the initiation of the first treatment period. In practice, this is frequently difficult to achieve because the pharmacologic and psychological effects of the first treatment often have a carryover effect on the response to the second treatment. This is especially true if the drug administered during the first treatment period has a long biological half-life. Theoretically, these objections can be minimized by imposing a sufficiently long washout period between treatments. The theory, however, is often more easily prescribed than achieved.

There are certain obvious caveats concerning the use of the crossover design. It should not be used in drug studies involving self-limiting diseases of short duration, or with treatments that result in rapid relief or cures because of the likelihood of the illness being resolved and symptoms alleviated before the crossover takes place. Parallel group studies are more popular than crossover comparisons because they present fewer problems. The parallel group study is probably a less complicated and expeditious way to double-blind and complete a study in a much shorter period.

A. Elements of a Protocol: A Checklist

The following items provide an outline of the factors that must be addressed in planning a protocol for all phases of clinical research (including bioavailability studies). Although some of the headings cited below may seem obvious, often they are completely overlooked or taken for granted by protocol designers/administrators.

1. Title page
2. Table of contents
3. Introduction
4. Bibliography
5. Objective
6. General
7. Risks
8. Confidentiality
9. Materials and methods
10. Study drugs
11. Assignment of study drugs
12. Dosage range

16. Duration of drug treatment
17. Concomitant medications
18. Case report forms
19. Laboratory assessments
20. Adverse experiences
21. Statistical handling of data
22. Overall duration of the study
23. Institutional Review Board (IRB)
24. Informed consent
25. Monitoring
26. Location of study
27. Location of laboratory testing facilities

13. Dosage schedule
14. Administration of study drugs
15. Labeling of study drugs
28. Investigator's obligations
29. Signature page
30. Amendments and addenda

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1. Title Page

Provide the full title of the study, including, if possible, a precise description of the study's objective. (If you feel that it would aid FDA reviewers in identifying the study, give the full name, including initials, of the investigator and, where applicable, co-investigators.) Many protocols are identified by a study number assigned by the sponsor; this number should be cited throughout the protocol where necessary, particularly if there is the possibility of confusion with similar studies being conducted at the same time and location. It is sound practice to have the sponsor's name and address listed on the title page. More than one sponsor may be using the same teaching hospital or institution to conduct other clinical trials on other drugs. The following is an example of a protocol title page:

A PHASE 2 DOUBLE-BLIND PARALLEL STUDY
OF DOSE TOLERANCE, SAFETY, AND EFFICACY
COMPARING DRUG A TO PLACEBO IN CONTROLLING
SYMPTOMS OF MILD TO MODERATE HYPERTENSION

Chief Investigator:

Co-investigator(s):

Study Number: Sponsor (Name and Address):

Date:

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2. Table of Contents

An interested investigator should read the entire protocol to understand the objective(s) of the study. However, sometimes certain sections of the protocol are of more interest than others to different participants conducting the clinical trial. A protocol may, for example, contain separate sections devoted to the interests of the project coordinator, a nurse, a psychologist, a cardiologist, and others. When one or more individuals have to refer quickly to a section of the protocol to clarify points concerning a particular procedure or method, they should be able to do so easily with the aid of a table of contents and its main headings, subheadings, and appropriate page numbers.

3. *Introduction*

The main point to cover in the introduction is the purpose for the investigation. Each clinical study should have a significant purpose that will be fulfilled at the conclusion of the study. No clinical study should ever use a patient population without the specific goal of knowing more about a product and its benefit to the patient. Also included in the introduction is a description of the specific diagnosis and special patient characteristics for each disease to be investigated.

An optional part of the introduction can include all significant past research and literature references on the drug being investigated; this should be carefully reviewed, summarized, and incorporated into the introduction. This section should include the following: all relevant published materials; preclinical information from the Investigator's Brochure; and any previously conducted, comparable clinical studies (with appropriate comment on the methods of observation and qualitative evaluations used in the other studies [i.e., design, placebo controls, active controls, and methods of data analysis]). Other points that should be considered for inclusion in the introduction include identity and potency of the drug(s) being used, study setting (nursing homes, psychiatric wards, outpatient clinics, etc.) and the rationale for using that setting. This should not be a repeat of a clinical brochure, but a summary of any knowledge about the drug based on completed evaluations. Many protocol writers consider the clinical brochure an adequate introduction to the protocol and the product being developed. However, it is always a concern that investigators don't always take the time to read voluminous clinical brochures, but they will read the introduction of a protocol.

One of the critical areas considered by the FDA in reviewing a clinical protocol is the merit of a clinical research investigation. The introduction should satisfy the reviewer that this study will attempt to produce a reliable solution to a scientific question about the drug being tested.

4. *Bibliography*

All interpretive commentary should be referenced in a bibliography, together with all of the citations of previous research. This will help the investigators feel comfortable using an experimental drug, especially when they have need for more detailed information.

5. *Objective*

The objective is the essence of a protocol. It should state explicitly the purpose of the clinical research project. One short statement should describe the type of study (i.e., open, double-blind, crossover) and why the study is being conducted. In addition, a brief description of the medications to be used, the indication(s) for effectiveness, and the type of patient population to be evaluated should be included. The objective should be stated succinctly, as in the following example: "The objective of this controlled, double-blind, parallel study is to evaluate the efficacy and safety of medication X versus medication Y in (diagnosis of disease) as found in an outpatient (or other) population." In one simple statement, the purpose of the study, the controls, the diagnosis of the patient population, and the setting where these patients will be observed have been presented. Objectives should reflect the phase or type of clinical research that will be conducted.

A phase 1 study with safety evaluations based on dose tolerance as its major objective would not necessarily be double-blinded; phase 2, 3, and 4 studies, on the other hand, would concentrate on dose tolerance and safety, as well as efficacy, and should always (when possible) be conducted using double-blind standards to guard against bias.

6. General

This section usually contains a condensed summary of the protocol. It can prove helpful to personnel charged with recruiting clinical research investigators and their staffs. In many cases, the first contact with a prospective investigator is by telephone. Initial reactions—interest or no interest—can be elicited by a reading of the general section of the protocol. It should offer a brief description of the study objective, the study design, the study duration, the evaluations needed for efficacy and safety, and the estimated amount of time required from the investigator, and his or her staff. More importantly, it should answer the question as to whether the investigator has the patient population that meets the inclusion and exclusion criteria of the study design. The preparation of a succinct general section can save hours of needless conversation describing protocol design and responsibilities of the investigator and staff.

7. Risks

Whereas risk is always a factor in all medical intervention, the relatively unknown magnitude of risk entailed in the use of a new investigational substance is the focus of much of the FDA's concern. The burden of proof for justifying the experimental use of an investigational drug lies with the sponsor. Documentation within the IND must be presented in an argument that makes it seem probable. This is heavily based on preclinical research in animals: the pharmacology and toxicology of the investigational drug that affirm that the drug is probably safe at a specified dose in the defined human population. It is sometimes appropriate to weigh the relative risks of untreated disease with the projected risks with use of the investigational drug. In any event, the methodology of the trial should minimize risks to the subjects so that potentially, the benefits will outweigh the risks.

8. Confidentiality

The doctor-patient relationship has traditionally entailed the right of the patient to complete confidentiality; Enrollment in a clinical trial should not compromise this right. Just as the staff in a physician's office is trained to understand that they must not breach a patient's right to confidentiality, any additional staff working with files of patients enrolled in clinical trials must also respect this confidentiality. Procedures by which patients can be numbered or identified by their initials and site number should be spelled out to ensure that there is no unnecessary disclosure of the identity of the participants in the study.

9. Materials and Methods

Under this heading, the following points should be listed and described:

a. Patient Sample

Provide a statement describing the total number of patients expected to complete the study; this number can include an estimate of treatment failures but should not include administrative dropouts. (If patients are transferred from inpatient clinics, if they relocate, or if they do not complete the study for any other reason [not drug related], they should not be included in the total.) Establish the number of patients that must complete the study and be part of the final statistical analysis. Additional patients should always be enrolled in a clinical study to make certain that, minus study dropouts, the required number of patients needed for meaningful statistical analyses are still available, and that administrative dropouts will not jeopardize numbers needed for the final statistical analysis.

b. Age Range

Include a precise age range for the study subjects. Do not allow an investigator to amend the age range during the course of the investigations; it should be established before the study is initiated and strictly adhered to. The age range for patients should be carefully selected according to the disease being investigated. It would not be advisable, for example, to study schizophrenia in patients aged 65 years or older; nor should mononucleosis be studied in patients 40 years of age or older, inasmuch as the disease is more prevalent in young adults. However, it should be noted that the age range in the final clinical studies for an NDA is the one that will eventually be included in the package insert.

c. Gender

Indicate whether or not males, females, or both sexes will be used in the study.

d. Patient Inclusion Criteria

This is one of the most important parts of protocol development. Describe the type of patient to be admitted into the study. The criteria for selecting patients must be clearly and accurately stated, whether the study calls for a specific diagnosis or a diagnostic profile of a symptom cluster; in either case, the diagnosis must be well established. (The FDA favors a protocol with a specific diagnosis.) Specifically state the symptoms to be rated for patients meeting the criteria of the study. It is up to the investigator to confirm and document the diagnosis with an accurate account of the medical history and a complete medical examination.

And finally, the following statement must be included in this section of the protocol: "Each patient enrolled should be fully eligible according to the protocol criteria. Each patient should also give every clinical and personal indication that he or she can be expected to complete the full course of the investigation." Otherwise they should not be enrolled. Nothing is more frustrating to a sponsor—or to the designer of a protocol—than to have patients drop or be dropped from a study because they do not meet criteria for entry, or they fall into categories that disqualify them from receiving the study medications, or they simply do not wish to continue in the study because their obligations for participation in the study were not clearly spelled out. Obviously, any patient has the right to withdraw from a clinical trial at any time, but it is up to the investigators to select study subjects they feel are most likely to complete the study and to avoid entering those with doubt.

e. Patient Exclusion Criteria

This part of the protocol must be very explicit. Any patient who by every reasonable expectation would be incapable of responding to a study drug or does not meet inclusion criteria must be ruled out. Patients with existing ailments that would prevent the study medication from showing its maximum therapeutic effect must be excluded from participation, as should any patient who is hypersensitive to the medications under investigation. The criteria should also exclude any patient whose medical history, physical condition, concomitant medications, or personal habits (e.g., smoking) might compromise the integrity of the data to be gathered during the clinical trial or might pose a safety concern. It must be remembered constantly when designing a protocol that this is an investigational study, not a routine medical visit!

The protocol designer must pay particular attention to the number of exclusions listed in the protocol; too many can make it extremely difficult to enter enough patients in the study, and too few can lead to compromised data.

f. Study Procedures

It is essential to the protocol to give the relative sequence of events that each patient will be expected to complete and to define each event thoroughly. Screening visits, baseline laboratory evaluations, day 1 of dosing, washout periods, postdosing evaluations, etc. should all be discussed and mapped out. A table or flowchart is usually helpful so that, at a glance, the events during the course of an investigational study can be seen in relation to each other and at the same time keep the investigators and the research staff on course.

Drug-free and washout intervals must be defined. Washout, dryout, predrug, run-in, and other similar periods must be carefully noted. They must be long enough to assure that any previous medications that might interfere or interact with the study drug will be eliminated from the patient's system before study drug administration. Washout periods are critical to the success of a study. They must be observed before a baseline evaluation is made and the study medication is administered. (Placebo responders must also be considered during the predrug evaluation period.)

There are, however, exceptions to the washout period conditions. For example, if a patient exhibits symptoms of sufficient severity to warrant not withholding treatment, this patient may be entered into the study even though the washout period is less than that specified. If a note to this effect is included in the protocol, the investigator should provide ample justification in the comment section of the case report form. In the monitoring of a study, patient records should be carefully checked for validity (acceptability) of the reasons for exemption from the full washout period.

Note: If a predrug symptom rating falls into the category of mild or moderate and a patient is entered into an investigation before the washout period is terminated, this predrug rating will not justify the patient's exemption from the medication-free period unless a valid reason is given by the investigator or is stated in the protocol.

10. Study Drugs

Include a complete description of the medication, including the lot number, to be used in the study. The generic as well as the trade name (if available) should be stated. Describe the form of the drug and placebo (i.e., capsules, tablets, injectable). Also provide the methods of preparation, especially for the placebo (lactose or sucrose fillers, for example). Detail as well the way the study medication will be blinded. In addition, the strength of the study medication must be stated in milligrams, grams, cubic centimeters, etc. The details that would be stated in a package insert should be provided. If a marketed drug is used as a control, the package insert for that medication should be included in an appendix to the protocol. The dose of each drug must be listed (e.g., "capsules containing

10 mg of drug X"). Medication used in a clinical trial must have all of its components completely listed by name and quantities.

11. Assignment of Study Drugs

In this section, it is important to do two things: outline the method of randomization so that the procedure is clear and is set out as a standard for all sites (in the case of multicenter trials); and make certain that the method of randomization is shown to be truly random and thus supportive of scientifically valid conclusions and equitable to the patients.

Prepare an explicit description of the actual assignment of the type or types of medication(s) used in the study. The opening statement could read, for example, numbers 01 to 100 will be assigned to the study medication bottles on a random basis, as determined by the use of a table of random numbers. Patients will then be assigned to bottles 01 to 100 in sequence, that is, the first patient admitted into the study will be assigned to the bottle marked 01, the second patient to the bottle marked 02, etc. (Numbers are assigned to bottles, and patients are assigned to numbered bottles.) When each patient is to receive only one bottle, this should be stated: "Each patient will be assigned one bottle of study medication. The bottle will contain a total of X capsules (or tablets, cc's, etc.) of study medication—a quantity sufficient to meet the maximum medication requirement as required by this study (X days or X weeks, etc.)." If medication is to be administered on a daily or weekly basis, for example, bottle numbers and the quantity in each bottle for that period should be specified. A reference to the type of randomization table used should be made and footnoted. The investigator should be aware of how the medications were randomized, for example, in blocks of 4, 6, 10, etc., so that he or she will strive to complete a block of patients. A note should be added stating: "To allow for possible attrition, sufficient drugs will be provided for X patients, a number beyond that required by the protocol." This point is important to explain, as it may not be immediately obvious why, if 50 patients are required to complete a study, the medication will be randomized for 70. This is necessary to allow for circumstantial attrition and patients dropped for administrative reasons.

12. Dosage Range

Describe the dosage range to be used in the study. If applicable, include daily minimum and maximum dosages; these should reflect recommendations in the manufacturer's package insert or the dose range established during the early phases of clinical research.

Be sure to correlate the phase of clinical research that is being conducted and the dosage range recommended; the range used in a phase 1 study is often much broader than that used in a phase 2 or 3 study.

Designed to measure dose tolerance and safety, phase 1 dose ranging should be initiated and augmented very conservatively. During phase 2, the suggested dose range will, for the most part, have been influenced by results derived from the phase 1 trials. The objectives of dose tolerance and safety in a phase 2 study often allow a dose range different than that described for phase 1 studies. The phase 2 studies reflect responses of diseased patients in contrast to those observed with normal subjects. Prior to the preparation of a phase 3 protocol, the minimum and maximum dosage(s) will have been determined from the phase 2 program. If not, it is almost invariably a sign that phase 2 clinical studies were not adequately conducted.

13. Dosage Schedule

This section addresses the question of when appropriate amounts of drug are to be administered: once daily (q.d.), twice daily (b.i.d.), every 4 hours (q4h), three times daily (t.i.d.), and so forth. If specific dosages are to be given in the morning or evening, or both, specific instructions should be provided.

14. Administration of Study Drug

A statement should describe how the drug is to be administered to or taken by the patient: with meals; before or after meals; with liquids or dissolved in specific juices; and so forth. These directions are extremely important, because they may affect dissolution and absorption rates, may cause gastric upset, or may interact with certain elements or foods.

15. Labeling of Study Drugs

The proper labeling of all medications is imperative all of the time; however, during a clinical trial, it is essential that the blinding of the study drugs be protected. Therefore, labels containing the code of study drugs should be designed so that no one involved in the study knows which medication is being administered or dispensed. The label having the code should bear the same patient identification as that appearing on the drug label on the bottle for the patient. The sealed labels contain decoding information and are to be opened only in the event of an emergency or an adverse experience necessitating identification of the drug.

Drug code labels come in many forms. One of the most reliable is the dual-labeled form, in which the code is covered by a mercury film that can be scratched off easily by a coin or similar blunt object to reveal the identity of the contents. Another effective type is the three-sided envelope: A B C in front and C B A in back. Section C contains the written code and is sealed to part B. If an emergency arises, the detached code label portion is immersed in warm water for 2 minutes and then peeled apart. If the A B C form is used, the investigator should remove and save the coded portion prior to dispensing the medication, and attach it to the case report form. These labels are to be returned to the sponsor at the conclusion of the study. If a code label is missing from a patient evaluation form, the sponsor may not accept that patient's data for statistical analysis.

All unused study drugs must be accounted for and returned to the sponsor at the completion of a study. All unused study drugs in unopened bottles should be checked by the investigator and the sponsor for an accurate count. This information should be recorded and kept in the investigator's file. While the investigator is responsible for drug accountability, it is unwise to rely solely on his or her calculations. It is recommended that the clinical research monitor either perform a drug count on-site or have the drugs returned to the sponsor's clinical pharmacy department for re-counting.

16. Duration of Drug Treatment

During protocol design, it is important to determine how long a drug should be evaluated before it can be determined as safe and effective. This decision is usually based on previous research or a history of clinical experience of the disease under investigation. Drugs must be administered, monitored, and evaluated long enough to demonstrate optimum therapeutic response. However, diseases that have a short duration (e.g., a cold) should not be studied longer than necessary. Evaluating a short-acting drug such as an antihistamine for 2 weeks in treating a cold is impractical (if more than 3 days are required for this type of drug to show effectiveness, it is pointless to continue treatment). In contrast, the effect of tricyclic amine antidepressants takes at least 2 to 3 weeks, and therefore patients should be observed for 3 to 6 months to judge the maximum efficacy of this type of medication. One of the most crucial determinations of how effective a drug can be relies on whether it is possible to administer the drug for the predetermined duration without dose-limiting side effects occurring, while still achieving the maximum therapeutic effect on the disease being treated.

17. Concomitant Medications

The protocol should list all medications that patients are allowed to receive simultaneously with the study drug. Any contraindicated medications or those that are to be excluded during the investigation because they might interfere or interact with the study drug also should be listed. It should be emphasized that patients who receive any kind of concomitant medication not permitted in the protocol will be dropped from the study, and their data will not qualify for inclusion in the final statistical analysis of efficacy.

Regarding other medications allowed during the study, the following or a similar statement may be useful: "Other medications that are considered necessary for the patient's welfare and that will not interfere with the study drug may be given at the discretion of the investigator. Administration of all concomitant medications must be recorded in the appropriate section of the case report form." If the investigator administers to a patient any drug that is determined to be similar to the one under investigation, that patient will be dropped from the study and will not be entered in the data to be submitted at the conclusion of the investigation.

18. Case Report Forms

All the data gathered on an individual patient during the course of a clinical trial is recorded on a patient's CRF. Designing an easy-to-complete, accurate case report form containing all the essential data can be an arduous task. All of the details pertaining to the safety and efficacy of the drug under study have to have a place on the CRF. Depending on the phase of clinical research, the study design, the drug's indication(s), and the parameters being examined, a CRF can be anywhere from 5 to 10 pages to literally hundreds of pages in length. (*Note*: the more complicated the CRF, the more chance of data inconsistency.)

The case report form is the vital record of a clinical trial. It is necessary to design the CRF to collect all the data required by the protocol. Carefully designed CRFs are essential for the following reasons:

As a means of checking the logistics, design, and practicality of the protocol
For later processing, analysis, and interpretation of the study data so that the results may be accurately reported
To record safety and efficacy data that are consistent from subject to subject or patient to patient
To check for protocol adherence and/or investigator compliance
To fulfill FDA requirements.

The design of the CRF is a collaborative effort of the investigator, study coordinator, clinical monitor, program manager, statisticians, and data management personnel.

a. Content of the Case Report Form

1. Have the questions on the CRF directly address those defined in the protocol. The data collected must support the questions that are to be answered by the statistical analysis.
2. Provide definitions for terminology and scales to obtain consistency in evaluations from CRF to CRF within a study, as well as across

studies. These definitions should appear directly on the case report forms to make them readily available to the investigator.

3. Do not include additional questions that address ancillary issues. The attempt to collect and record too much information often leads to carelessness and lack of enthusiasm by the trial participants. The more that is asked for, the more variability will occur in the answers.
4. Questions should be asked directly and unambiguously free from jargon.
5. In long-term studies, the CRF may be formatted in sections and used for each visit or group of visits. This helps to decrease the likelihood of ambiguity in recording when an event occurs, as well as to help expedite the flow of data inhouse and through data processing.
6. Order the questions on the CRF logically, following the order in which a physician would ordinarily collect data. Separate questions that routinely would be asked by a study nurse from those that would be asked by the clinical investigator.
7. Be clear on how precise answers should be—should a value be rounded or carried to one or more decimal places? Lack of clarity here creates some doubt in the study recorder's mind; the resulting inconsistencies also increase the difficulties for the data processing staff. Collect direct numerical measurements, where possible, rather than broad categorical judgments. This usually improves overall consistency, especially across studies.
8. When questions include comparative terms, use positive terms such as better, bigger, and more, rather than negative terms such as worse, smaller, or less. Research has shown as much as a 20% difference in accuracy when positive terms are used.
9. Use design techniques that make the form easy to read and complete:
    - Balance white space with text. Make the form aesthetically pleasing, not cluttered.
    - Use check-off blocks (coded responses) wherever possible. Checking a block is less time consuming and error prone than entering a value or term.
    - Block sections of the form to make them easy to locate and complete.
    - Use variations in size and attributes of type (e.g., bold, italics, underlining) for headings and for emphasis of important questions.
    - Highlight the areas of the form where the investigator is expected to make entries. This decreases the chance that the investigator will overlook a question and helps during the inhouse review and processing of the data.
    - Keep calculations to a minimum.

- Alphanumeric fields (such as for adverse effects) should be sized to hold the largest possible response. Include instructions for filling out the CRF (e.g., use black ink, print, etc.).

19. Laboratory Assessments

Through laboratory determinations and the subsequent review of this data, the safety of a drug can be adequately assessed and, in some instances, the efficacy can be measured. Laboratories usually provide normal ranges with appropriate notations to highlight values outside the normal ranges. These are then reviewed to determine whether the abnormality or deviations are clinically significant or severe enough to cause concern for the safety of the patient taking the study drug. Safety evaluation criteria can include such determinations as sequential multiple analysis computer (SMAC) tests, CBC, urinalysis, vital sign monitoring, EEGs, ECGs, CAT scans, MRI, and radiologic examinations, including barium enemas and endoscopies. Many other tests capable of providing objective safety measurements may be considered. These results, coupled with any signs and symptoms attributed to drug reactions, will help complete the overall picture of a drug's safety profile. Many of the safety parameters, in most instances, do not reflect the efficacy of a drug. Whereas drugs with a spotless safety profile may be more desirable, therapeutic efficacy, in balance with an acceptable safety profile, is, after all, the more realistic goal.

Safety and efficacy evaluations may be objective or subjective. Objective evaluations are simpler to record, because they represent true values of drug response for safety and efficacy.

Objective values (numerical, photographic documentation, etc.) are easily recorded; for example blood pressure, pulse rate, measurements of lesions seen on endoscopy, etc. It is more difficult to accurately and consistently measure subjective impressions of improvement of symptoms, such as a reduction in pain or psychiatric disorders, by measuring and rating cognitive functions or feelings of well being. Proper standardization of the symptoms to be evaluated is essential. Although there is some confidence in using certain subjective, validated evaluations to distinguish between improvement and deterioration, it is often difficult to have the results unanimously accepted. One approach to measuring subjective evaluations with unknown scales is to ascertain that there is an acceptable explanation for quantifying, the severity or improvement that the investigator is evaluating. For example, if a symptom such as pain is being measured using a 7-point scale (from 0 = absent to 7 = extremely severe), the interim points may be designated as very mild, mild, moderate, moderately severe, and severe, each term being precisely defined. As an example, the type of definitions, listed below, are designed to reduce bias (variables) and increase accuracy in scoring the results. In other words, a numeric value is placed on a degree of pain that corresponds to a definition. By using this method to rate subjective symptoms, we gain consistency of data, especially when the study is multicenter.

1 = **Absent:** feels no pain
2 = **Very Mild:** feels pain once a week
3 = **Mild:** feels pain < three times per week
4 = **Moderate:** feels pain every day, but not severe enough for medication
5 = **Moderately Severe:** feels pain every day and needs mild pain medicine for relief
6 = **Severe:** feels pain all the time and needs strong pain medicine for relief
7 = **Extremely Severe:** feels pain all the time and gets no relief from pain medication

Of course, variations in defining degrees of severity of any subjective rating is totally dependent on the creator of the scale and the scope of the overall objective of the study.

20. Adverse Experiences

The protocol should include an adverse experience statement, such as "All adverse experiences occurring during the study must be reported on the drug reaction record provided in the patient case report forms." The drug reaction record is a complete questionnaire that covers all pertinent items concerning adverse experiences. (See Chapter 9.)

In addition, there should be a procedure for reporting serious, fatal, and life-threatening reactions expeditiously to the sponsor. This will enable the sponsor to make any changes in the protocol necessary for safety and to report the applicable adverse experiences to FDA within the required time frame. This is discussed in Chapter 9, "Adverse Reactions and Interactions of Drugs." Most protocols require that unexpected and severe, life-threatening, or fatal adverse experiences be reported immediately by telephone to the sponsor; a "24-hour" telephone number must be included in every protocol. The information provided on the drug reaction should be complete enough to enable the sponsor to provide the FDA with the proper and legal material necessary for reporting adverse experiences.

21. Statistical Handling of Data

The statistical handling section of the protocol must be finalized before an investigational study begins. Draft protocols should be reviewed and discussed with a biostatistician before they are finalized and presented to clinical investigators. Early input from a biostatistician is vital in the planning and writing stage of a protocol and leads to the success of a clinical research project. The CRFs should be developed and coded with statisticians before printing; this will facilitate data entry and expedite data processing. Requirements set forth in the protocol require careful planning and adherence to procedures. This will generate the type and quantity of scientific data necessary to achieve statistically valid documentation that will confirm the safety and efficacy of a drug. The statistical handling of the data is an integral part of the research protocol and is designed in the early planning stages of the study. It cannot be an afterthought when a mass of data has already been collected. The FDA will not accept the clinical data of any phase study if the statistical analysis methodology is not incorporated into the protocol before the initiation of the study.

22. Overall Duration of the Study

The maximum allowable time required by an investigator to complete the evaluations of all patients entered into the study should be clearly stated. The agreed-upon schedule should be strictly observed. Be realistic in your expectations. If an investigator estimates that he or she can handle 50 patients in 1 year, it may be safe to assume that it may take 2 years to complete the investigation. Some investigators do not realize how much work is required in completing the CRFs for the number of patients necessary to conclude a clinical trial successfully. The timetable described in the protocol must be reviewed with the investigator so that the time commitment is fully understood. If a flow chart is created, use it to demonstrate how many evaluations have to be completed over a defined period. For example, if a study calls for the entry of five patients per week and four or five CRF pages for that patient's entry (e.g., a physical, a history, a laboratory examination, and baseline determinations) and, in subsequent weeks, the trial calls for two or three evaluations per week, by the third week an investigator will have 16 to 21 evaluations. In a 50-patient study with each patient evaluated for 5 weeks, by the fifth week, the investigator will have 28 to 37 evaluations. It is apparent, then, that it is more practical for the primary investigator to enter fewer patients over a longer period and to persevere in completing the study rather than be faced with an impossible burden of work, deadline, and failure. It should be emphasized to the investigator that patients meeting the criteria of the protocol are not the same as in clinical practice, but scientific research and adherence to the protocol require a different discipline.

23. Institutional Review Board

A formally recognized and certified IRB must review the proposed clinical research practical to determine whether the relative safety and anticipated benefits to subjects/patients are adequately and fairly represented in the protocol design. If the research is to be done at a large hospital or teaching institution, it is likely that there is an affiliated IRB. Independent, certified IRBs are used at sites that lack their own IRB. A protocol used for a multicenter trial must be reviewed by an IRB for each site participating in the program. All protocols used in clinical research must have an IRB approval before drugs may be administered to patients entering a research study.

No clinical study plan is complete unless all the necessary precautions have been taken to protect the safety and rights of the patient. All studies conducted in the United States must be designed and carried out in accordance with Parts 50 and 56 of Title 21 of the Code of Federal Regulations (CFR), the regulations concerning the safety and rights of patients. For foreign investigations, ICH guidelines must be followed.

It must be remembered that an IRB will consider the following principal ethical requirements of a clinical research study before allowing the research program to start:

1. The risks to participants are minimized and are reasonable in relation to the anticipated benefits.
2. Selection of patients is equitable.
3. Appropriately worded and documented informed consent is obtained from each prospective participant or from a legally authorized representative if the participant is considered unable to give such consent.
4. The research plan makes appropriate provisions for monitoring the safety of the participants.
5. The privacy of the participants and confidentiality of the data will be maintained.
6. That the protocol objective will conclude a benefit for patients suffering with the disease under investigation.

24. Informed Consent

Some institutions have a preferred format for the informed consent form to be executed by patients within their own institution. The purpose of all such forms is to ensure that no experimentation is carried out on people who are unaware or unwilling to participate in an investigational clinical program. As this is a crucial tenet of modern investigational medicine, the protocol must specify that each patient must execute an informed consent document prior to enrollment in the study, randomization, and administration of any drug. In the case of a participant who is considered incompetent, a legally authorized representative must execute the document. Children under the age of 18 must have a parent or guardian sign the informed consent. These consent forms become part of the permanent patient records to be kept available for FDA inspection (see Chapter 10).

25. Monitoring

The following statement should be included in all study protocols: "At regular intervals throughout the study, the investigator will allow a representative of the sponsor's monitoring team, or the sponsor's designate, or a representative of the FDA to inspect all case report forms and corresponding portions of an enrolled patient's original office and/or hospital medication records. These inspections are for the purpose of verifying adherence to the protocol and the completeness and exactness of the data being entered on the case report forms."

The monitor of a clinical study (typically called a clinical research associate, or CRA, in the pharmaceutical industry) has to confirm that all of the necessary information requested on the CRF has been recorded. During a site visit, the monitor should be alert to the items on the CRF that are central to the study objectives. In an anxiety-depression study, for example, the most important symptoms are anxiety, tension, depression, or other anxiety-depression-related symptoms. These must be carefully noted and documented. The CRA should notice any changes recorded during the course of an investigation that indicate trends across the participating patient population. If there are significant rating changes after a certain number of weeks or after an assumed drug effect, these should be carefully documented and discussed with the investigator. A completed evaluation form for every patient in a clinical study is of paramount importance.

It is also the monitor's responsibility to account for all concomitant medications. Unfamiliar drugs should be cross-checked in the *PDR* to determine if any component(s) of the medication taken concomitantly with the investigational drug violates the protocol. All brand and generic names of drugs should be legible and identifiable. Monitors must assure that every adverse event has been reported and documented properly.

Other items, such as dosage titration information, should be examined, recorded, and (when applicable) reported with comments as to the reasons for these changes. Any incomplete item on a CRF must be explained, and a signed and dated statement from the investigator substantiating the reasons for the incomplete entry must be obtained. Any problems a monitor encounters during a clinical study should be discussed as soon as possible after the study has begun, these should be expeditiously resolved and noted.

26. Location of Study

List the investigator(s) name(s), address(es), and telephone number(s) where the study is to be conducted. If more than one location is involved (institutions, universities, and other medical offices), provide their locations as well.

27. Location of Laboratory Testing Facilities

List the names, addresses, and telephone numbers for all test laboratories involved in the study. An investigator must be able to contact laboratory personnel at all times. The protocol must include a record of where laboratory testing is being conducted. The laboratory director's CV and the laboratory's certification number have to be kept on file.

28. Investigator's Obligations

When agreeing to participate in the sponsor's clinical trial, an investigator is making several contractual agreements that must be clearly understood. The protocol must be adhered to, including the enrollment criteria, the blinding procedures, and the meticulous and timely record-keeping. A realistic estimate of the number of eligible patients the investigator will be able to enroll and follow-up will help to minimize the difficulties of conducting rigorous clinical investigation. To the extent possible, the agreed-upon time frame for completion of the study should be adhered to. It is also advisable to receive written assurance from the investigator that he or she agrees to conduct the study according to the protocol design and will adhere to the GCP regulations (21 CFR Part 312).

29. Signature Page

Allow space for the investigator's signature and the date the agreement is signed. The sponsor's clinician also should sign off on the protocol.

30. Amendments and Addenda

a. Amendments

Amendments to protocols have created a lot of controversy through the years. According to 312.30 in the CFR, any change in a phase 1 protocol that significantly affects the safety of subjects, or any change in a phase 2 or 3 protocol that significantly affects the safety of patients, the scope of investigation, or the scientific quality of the study requires an amendment to the protocol. Some examples of these changes are increase in drug dosage, duration of exposure of individual subjects or patients to a drug beyond that stated in a protocol, or increase of study population size. Other examples are adding or dropping a control group, adding a new test or procedure that is intended to improve monitoring for, or reduce the risk of, side effects or adverse events, or, conversely dropping a test intended to monitor safety. Overall, any significant change in the design of a protocol that requires doing something that may affect the patient's safety requires an amendment.

Any change that would apply to any of the above-stated items must have approval from the FDA, and should be submitted as an amendment to the FDA with written approval from an IRB before its implementation. At the same time, if there is a change in the protocol intended to eliminate an apparent hazard to subjects or patients, it may be implemented immediately, provided that FDA and the IRB are subsequently notified of a protocol amendment. It is important to remember that all protocol amendments to the FDA should be properly identified and labeled "Protocol Amendment: Change in Protocol." In the case of a change in a protocol, a brief description of the change in reference to the submission that contained the original protocol should be submitted with the amendment. In other instances, when new investigators are added to carry out a previously submitted protocol, the sponsor shall notify the FDA by an amendment within 30 days of the investigator's being added and await IRB approval.

Although amendments can be submitted at any time during a clinical investigation, it behooves the investigators not to amend the protocol unless it is absolutely necessity to expedite the acceptability of patients entering into a study, that is, the deletion or addition of significant requirements for subject or patient eligibility. The reason is that statistically, it is very difficult to deal with changes made from the original protocol design in the final statistical analysis. The analysis of these data must reflect the results of the patient's evaluations before and after amendments. In the analysis of the results of all patients in studies with or without amendments, it is difficult to conclude results based on different protocol designs, such as, patients previously admitted to the study with no history of hepatic disease and subsequently, through an amendment, allowing patients into a study having a hepatic disease 1 year before entering the study. It is imperative, therefore, to abide by the initial recommendation of this chapter, that is, whenever possible, do not change a protocol once it has been designed with diligence, intelligence, and expertise in meeting the original objectives of the clinical study plan. Amendments should never be done after 49% of the patients have entered the study unless to further guard the safety of the patient.

b. Addenda

Often when protocol designers speak of addenda, they confuse them with amendments. There is a distinct difference from amendments, which are significant changes that can affect the safety of the patient, the implementation of procedures of a protocol, and the results obtained from a protocol. Addenda are simply additions to the protocol that do not change the safety measures of the patients or the original study protocol. For example, if specific quantities of blood are being drawn from a patient and another laboratory test is added using this same blood sample, this is an addendum. This typical addendum to the protocol does not change any procedures from the original protocol and does not affect the safety of the patient. It is usually an additional test that could be reported in the final statistical analysis and clinical report.

Addenda to the protocol do not have to be submitted to the FDA or IRB committees for approval.

VIII. SUMMARY

Many approaches and different styles are useful in the development and preparation of a sound clinical research study protocol. The foregoing guidelines can be modified to suit the applicant's needs and objectives. No matter which path is mapped out, it is imperative that investigators abide by the final protocol. Strict adherence to a well-designed protocol will result in research projects that reflect the stated objectives in the required amount of time leading to successful and definitive conclusions.

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9

Adverse Reactions and Interactions of Drugs

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I. INTRODUCTION

There is an old but nonetheless true dictum in pharmacology: no drug has a single action. Unfortunately, multiple actions of therapeutic drugs are not always in the best interest of the patient. In addition to the primary therapeutic effect for which a drug is prescribed, the likelihood exists for the emergence of concurrent or delayed, unwanted, and potentially harmful effects–adverse reactions—which may be due to other known pharmacologic or toxic effects of the drug. Such reactions also may be attributed to some idiosyncrasy in certain individuals. Any active drug, therefore, may be a double-edged sword, doing good on one hand and perhaps harm on the other.

With the recent impressive advances in pharmacology and the ability to synthesize new, complex, and more potent drugs without commensurate knowledge of how and under what conditions they act in humans, the question of adverse reactions (ADRs) and the interactions of drugs has become an increasingly serious aspect of modern therapeutics. It is not surprising, therefore, that drug legislation in most countries is concerned as much with the safety of drugs and devices as with their efficacy. As a result, this aspect of drug evaluation is demanding more and more attention from those involved in drug, device, and vaccine research and development, particularly with respect to unwanted or toxic effects.

According to the International Committee on Harmonization and Good Clinical Practice guidelines (ICH/GCP), in the preapproval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered ADRs. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (i.e., the relationship cannot be ruled out). Regarding marketed medicinal products, an ADR is a response to a drug that is noxious and unintended and that occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of diseases or for modification of physiologic function (1).

Because of the difficulty in obtaining accurate records, the true incidence of adverse reactions to drugs in the population at large is unknown. In the April 15, 1998, issue of the *Journal of the American Medical Association*, Lazarou and colleagues (2) attempted to assess the incidence of serious and fatal ADRs in hospitalized patients by searching four electronic databases and selecting 39 prospective studies from hospitals in the United States. The overall incidence of serious ADRs was 6.7% and of fatal ADRs, 0.32%. Indeed, ADRs were between the fourth and sixth leading cause of death in hospitalized patients. The incidence of ADRs of all severities (including serious and nonserious) was 10.9%. Although the authors recommend that the results be reviewed with circumspection because of heterogenicity among studies and small biases in the samples, they concluded that ADRs represent an important clinical issue.

The necessity of a clear understanding of the total pharmacology of therapeutic drugs, particularly of their potential for inducing ADRs either alone or in concert with other drugs, needs no further emphasis. It has become a major concern for those responsible for developing, prescribing, and dispensing therapeutic agents.

II. CLASSIFICATION OF ADVERSE DRUG REACTIONS

In general, adverse reactions to a drug may be either dose dependent or independent. Although both types may be produced to a greater or lesser extent by the same drug, dose dependency is a convenient and satisfactory method for classification.

A. Dose-Dependent Adverse Reactions

If an active drug is administered in sufficiently large doses, eventually all individuals will manifest adverse reactions. The dosage levels at which the reactions occur, however, may vary considerably from individual to individual. Dose-dependent adverse reactions are usually specific for the drug concerned. They can be categorized as follows: (a) known for unwanted pharmacologic effects (e.g., the anticholinergic effects of the phenothiazine tranquilizers); or (b) exaggerated therapeutic effects (e.g., orthostatic hypotension with antihypertensive drugs such as clonidine and guanethidine when these agents are taken at higher than usual doses); or (c) reactions unrelated to the therapeutic effects (e.g., ototoxicity produced by excessive doses of streptomycin).

Dose-dependent adverse reactions are influenced by a number of physiologic and pathologic factors that have little or no bearing on dose-independent reactions. Prominent among these factors are liver and kidney disease, enzyme abnormalities, and drug interactions that may affect absorption or involve competition for transport binding sites of action, certain physiologic conditions altering drug excretion, and age. Dose-dependent ADRs are often more prominent at the chronologic extremes of life. The fetus, the newborn infant, and the aged are more susceptible than young adults and the middle aged to the effects, good and bad, of many drugs.

1. Pregnant Women

The fetus is particularly susceptible to the toxic effects of certain drugs that pass the placental barrier. The ill effects of such drugs may vary according to the stage of pregnancy at which they are administered. Drugs with teratogenic properties, for example, given during the first trimester—the period of fetal organogenesis—may cause congenital abnormalities. Moreover, susceptibility of particular organs to drug-induced malformation depends on the time the drug is given during the first trimester. The critical teratogenic period for the nervous system is from gestation days 20–40, for the limbs, gestation days 24–36, and for the eye, gestation days 24–40. Drugs given to the mother after the first trimester may affect the growth or function of normally formed fetal tissues or organs (3). The classic example of a drug with teratogenic activity in humans is thalidomide, which is associated with phocomelia; this stimulated the drug regulatory bodies in many countries, including the United States, to adopt more stringent controls on new drug development.

Antineoplastic drugs such as 6-mercaptopurine, methotrexate, cyclophosphamide, and aminopterin administered in early pregnancy have produced various congenital malformations. Cytotoxic drugs also have induced fetal malformation and early abortion of malformed fetuses (4–6).

Corticosteroids administered during the period of fetal organogenesis have been associated with anencephaly (7) and carry a high risk of inducing cleft palate. Lysergic acid diethylamide (LSD), among other hallucinogenic drugs, has been shown to produce chromosomal damage; on less certain evidence, its use during pregnancy may result in congenital anomalies.

The more frequently prescribed drugs that have been reported to affect growth and function of organs when given to the mother after the period of fetal organogenesis, or to the newborn infant, are discussed below.

a. Antibacterial and Antibiotic Drugs

Sulfonamides are extensively protein bound. If these drugs are administered to mothers immediately before delivery or to the premature or full-term infant while there is physiologic hyperbilirubinemia, they may displace bilirubin from plasma protein, causing severe jaundice or kernicterus (8).

Chloramphenicol is not adequately detoxified and excreted by the fetus or the premature infant. Administration of this antibiotic to the mother shortly before parturition may produce gray coloration of the infant's skin with associated muscle hypotonia and circulatory collapse, known as "the gray baby syndrome" (9). (This side effect is more noted in premature infants.)

b. Anticoagulants

Coumarin and indandione derivatives given during pregnancy cross the placental barrier. Even though the maternal prothrombin times remain normal, the use of these anticoagulant compounds may result in fetal death owing to hemorrhage in utero (10) or to intracranial bleeding caused by birth trauma (11).

c. Antithyroid Drugs

Congenital goiter and neonatal hypothyroidism may occur if thiouracil drugs are administered during pregnancy (12).

d. Oral Hypoglycemia Drugs

Intrauterine fetal death and prolonged symptomatic neonatal hypoglycemia have been reported after treatment of the mother with sulfonylurea drugs (13,14).

e. Cardiovascular Drugs

In general, cardiovascular drugs have the same but exaggerated effects on the fetus as on the mother. Beta-receptor stimulants (e.g., isoproterenol), and beta-receptor-blocking agents, such as propranolol, may respectively cause significant fetal tachycardia or bradycardia. Norepinephrine and other alpha-receptor stimulants given during pregnancy may induce constriction of the uterine vessels, and thus indirectly result in fetal asphyxia.

f. Anesthetics, Analgesics, and Hypnotics

If anesthetics, analgesics, and hypnotics are given during labor, they can adversely affect the newborn child by inducing respiratory depression and neonatal asphyxia.

The appearance of typical withdrawal symptoms in the newborn infant of an opiate-addicted mother has been well documented.

So that the aforementioned teratogenic effects can be avoided, pregnant women should, in general, be excluded from clinical trials in which the drug is not intended for use in pregnancy. Before the inclusion of pregnant women in clinical trials, all the reproductive toxicity studies (15,16) and the standard battery of genotoxicity tests (17) should be conducted. In addition, safety data from previous human exposure are usually needed. If a patient becomes pregnant during administration of the drug, treatment should generally be discontinued if this can be done safely. Follow-up studies of the pregnancy, the fetus, and the child are very important. For clinical trials of a medicinal product for use during pregnancy, follow-up studies of the pregnancy, the fetus, and the child are important.

2. Nursing Women

In investigations in nursing women, excretion of the drug or its metabolites into human milk should be examined where applicable. When nursing mothers are enrolled in clinical studies, their infants should be monitored for the effects of the drug.

3. Women of Childbearing Potential

The patients included in clinical studies should, in general, reflect the population that will receive the drug when it is marketed. For most drugs, therefore, representatives of both sexes should be included in clinical trials in numbers adequate to allow detection of clinically significant sex-related differences in drug response.

Appropriate precautions should be taken in clinical studies to guard against inadvertent exposure of fetuses to potentially toxic agents and to inform subjects and patients of potential risk and the need for precautions. In all cases, the informed consent document and the investigator's brochure should include all available information regarding the potential risk of fetal toxicity.

In general, it is expected that reproductive toxicity studies will be completed before there is large-scale exposure of women of childbearing potential (i.e., usually by the end of phase 2 and before any expanded access program is implemented).

Except in the case of trials intended for study of drug effects during pregnancy, clinical protocols should also include measures that will minimize the possibility of fetal exposure to the investigational drug. These would ordinarily include provisions for the use of a reliable method of contraception (or abstinence) for the duration of drug exposure (which may exceed the length of the study) and the use of pregnancy testing (beta human chorionic gonadotropin [HCG]) to detect unsuspected pregnancy before study treatment begins.

4. Geriatric Population

The geriatric population is arbitrarily defined as comprising patients 65 years or older. The older the population likely to use the drug, the more important it is to include the older age range, 75 years and older. For drugs used to treat diseases not unique to, but present in the elderly, a minimum of 100 patients usually would allow detection of clinically important differences between the elderly and younger patients with respect to efficacy as well as adverse reactions.

Elderly individuals often develop adverse reactions to drugs at dosage levels well tolerated by younger persons. These reactions may be due to an age-related increase in sensitivity to drugs or impairment of detoxification (metabolism) and excretion functions.

Sedating, hypnotic, tranquilizing, and tricyclic antidepressant drugs are prone to precipitate confusional states in the elderly, particularly if there is preexisting evidence of impairment of cognitive function (18–21). Extrapyramidal symptoms such as akathisia and parkinsonism are more common in the elderly than in younger patients treated with phenothiazine tranquilizers, particularly piperazine derivatives, butyrophenones, and tricyclic antidepressants (22). Furthermore, these psychotropic agents and other drugs with anti-intestinal motility effects in the elderly result in troublesome constipation, fecal impaction, and occasionally paralytic ileus (23,24).

Digitalis toxicity is not infrequently encountered in geriatric patients given digitalizing doses considered normal for younger patients. The elderly also are more likely to develop hypokalemia with the potassium-wasting diuretics. If these drugs are given concurrently with digitalis, the therapeutic regimen further increases the risk of digitalis toxicity.

It has also been reported that heparin administered to women older than age 60 renders them approximately 50% more susceptible to bleeding complications than men similarly treated (25).

5. *Pediatric Population*

The pediatric population consists of four pediatric subgroups: neonates (birth up to 1 month), infants (1 month to 2 years), children (2–12 years), and adolescents (13–16 years).

Many drugs labeled only for adult use are in fact widely used in pediatric patients for the same indications. Less than half the drugs approved for treatment of HIV infection carry any pediatric safety or effectiveness information. Almost no information on use in patients younger than 2 years of age is available for most drug classes (26).

Some ADRs occur in children because of inadvertent drug overdoses or other drug administration problems, such as inadequate treatment, that could have been avoided with better information on appropriate pediatric use. This is of particular concern in infants and neonates, because correct pediatric dosing cannot necessarily be extrapolated from adult dosing information using an equivalence based either on weight (mg/kg) or body surface area (mg/m^2). Potentially significant differences in pharmacokinetics may alter a drug's effect in pediatric patients. The effects of growth and maturation of various organs, maturation of the immune system, alterations in metabolism throughout infancy and childhood, changes in body proportions, and other developmental changes may result in significant differences in the doses needed by pediatric patients and adults.

One of the earliest cases in which serious adverse events were observed in neonates after administration of a drug that had not been adequately studied in pediatric patients was the development of "gray baby syndrome" from chloramphenicol, an antibiotic (27). After an initial report of five deaths and a subsequent report of 18 deaths in neonates, it was learned that the immature livers of these infants were unable to clear chloramphenicol from the body, allowing toxic doses of the drug to accumulate. Other cases in which inadequately studied drugs have resulted in serious adverse effects in pediatric patients include teeth staining from tetracycline, kernicterus from sulfa drugs, withdrawal symptoms after prolonged administration of fentanyl in infants and small children, seizures and cardiac arrest caused by bupivacaine toxicity, development of colonic strictures in pediatric cystic fibrosis patients after exposure to high-dose pancreatic enzymes, and hazardous interactions between erythromycin and midazolam (26–37). Many such adverse reactions could be avoided if pediatric studies were conducted before drugs were widely used in pediatric patients.

In the future, the FDA will require pediatric studies if the drug product will be widely used in the claimed indication and the absence of adequate pediatric labeling could pose significant risks to pediatric patients. Studies will also be required if the drug product is indicated for a very significant or life-threatening illness, but additional dosing or safety information is needed to permit its safe and effective use in pediatric patients.

6. *Enzyme Abnormalities*

Enzyme abnormalities may be inherited or acquired. Some of the more important inherited enzyme abnormalities are discussed below. The acquired conditions are dealt with later in this chapter under Drug Interactions.

a. Inherited Enzyme Abnormalities

It is becoming increasingly evident that a number of adverse reactions to drugs are due to genetically transmitted inborn enzyme abnormalities or deficiencies. The best known example of this category is the hereditary relative deficiency of the enzyme glucose-6-phosphate-dehydrogenase (G-6-PD), which occurs in 5% to 10% of Mediterranean littoral races, blacks, Pakistanis, and Sephardic Jews. This condition renders affected individuals susceptible to acute hemolytic anemia when they are exposed to such drugs as primaquine, phenacetin, aspirin, chloramphenicol, nitrofurantoin, and sulfonamides, and to the fava bean.

Other hereditary enzyme deficiencies that may result in adverse reactions to certain drugs are comparatively rare, often familial, and of worldwide distribution. Examples of these conditions are pseudocholinesterase deficiencies in certain people who, when given succinylcholine or suxamethonium, develop a profound, general neuromuscular blockade with apnea (38).

Tuberculous patients lacking in liver N-acetyl transferase who are treated with isoniazid are likely to develop polyneuritis (39). An enzyme abnormality is also responsible for the precipitation of acute intermittent porphyria by the barbiturate drugs (40). Likewise, the rare hereditary resistance to coumarin anticoagulant drugs is thought to be due to an enzyme deficiency (41).

7. Liver Disease

Biotransformation of most drugs takes place in the liver. A disease that affects liver function, therefore, may impair metabolism and inactivation of drugs. This will increase the degree and duration of action of a drug to the extent that exaggerated therapeutic effects and adverse reactions may occur at normal therapeutic dose levels. The list of therapeutic agents so affected is long and varied. It includes such widely used drug groups as phenothiazines, barbiturates, narcotic analgesics, corticosteroids, and oral anticoagulants. Also, patients with markedly reduced liver function are especially prone to develop hepatic encephalopathy when given potassium-wasting diuretics, narcotic analgesics, and central depressant medications.

Drugs also may be the cause of impaired liver function. Direct hepatotoxicity is induced by known hepatotoxins that produce fatty infiltration, degeneration, and widespread necrosis of the liver cells. Carbon tetrachloride, arsenic, gold, mercury, iron, phosphorus, some insecticides, and industrial solvents all have a dose-dependent, direct toxic effect on the liver. Fortunately, except perhaps when taken in massive overdoses for suicidal purposes (such as acetaminophen), direct hepatotoxicity with therapeutic drugs is rare. This sinister potential of hepatotoxicity is usually detected in preclinical animal studies, and the drug candidate is then rejected on this account. A dose-dependent form of drug-induced hepatitis, clinically similar to viral hepatitis, may be produced by halothane anesthesia, particularly after multiple exposures (42). Cholestatic jaundice, the most common manifestation of drug-induced liver dysfunction, is essentially an allergic-type phenomenon and is discussed under dose-dependent reactions.

8. Renal Disease

If renal function is sufficiently impaired, unchanged drugs and their metabolites that are primarily excreted in the urine can be retained in the circulation to a greater or lesser degree. As a result, the therapeutic or adverse effects of the unchanged portion of the drug may be exaggerated and prolonged; additional adverse reactions due to accumulating metabolites may also appear. Impaired renal function markedly increases the likelihood of ototoxicity due to the administration of the aminoglycosides streptomycin, kanamycin, and gentamicin. The likelihood of toxic effects of normal doses of digitalis preparations on the heart are greatly increased in patients with renal insufficiency.

B. Dose-Independent Adverse Reactions

Occurring less frequently than dose-dependent reactions, dose-independent incidents are largely confined to allergic reactions in persons sensitized by previous administration of the same drug, or by another drug with cross antigenicity with the original medication. Allergic responses also may occur in individuals who are uniquely susceptible to relatively weak antigens or who develop sensitivity on the first use of a drug—the so-called idiosyncratic reaction.

Allergic responses to drugs are mediated by the release of histamine or histamine-like substances, and they commonly present as skin rashes, particularly urticaria. More serious hypersensitivity responses include bronchospasm or the acute, explosive anaphylactic reaction with cyanosis and cardiovascular collapse. A delayed reaction known as serum sickness, although more often associated with such drugs as the penicillins and cephalosporins rather than with serum, manifests clinically 7 to 10 days after receiving the drug or serum as fever, malaise, joint pains, and urticarial skin rashes.

Blood dyscrasias, mostly dose independent, are among the most important allergic-type adverse reactions to drugs. Aplastic anemia is a serious but rare (presumably) idiosyncratic reaction. It has been reported in association with chloramphenicol, quinacrine, phenylbutazone, mephenytoin, gold compounds, and potassium chlorate. Hemolytic anemia, thrombocytopenia, and agranulocytosis may result from an unusual, acquired sensitivity to a variety of widely used drugs including aminopyrine, phenylbutazone, phenothiazines, propylthiouracil, diphenylhydantoin, penicillins, chloramphenicol, sulfisoxazole, and tolbutamide.

Certain collagen-like diseases are caused by hypersensitivity reactions to drugs. Hydralazine, and particularly procainamide, may produce a clinical picture similar to systemic lupus erythematosus (43). A number of cases of polyarteritis nodosa have developed during treatment with guanethidine and after repeated exposure to the sulfonamides, penicillin, and iodides (44). Nephropathy has been reported following high doses of methicillin and benzylpenicillin (45).

Dose-independent, drug-induced liver dysfunction (cholestatic jaundice) is not an unusual adverse reaction. Caused by a number of different, commonly used drugs, cholestasis is a hypersensitivity reaction that primarily affects the biliary canaliculi, causing an intrahepatic obstructive jaundice. An alteration in bile secretion by the hepatocytes, however, may also be involved (46). Among the drugs known to be responsible for the development of cholestatic jaundice are the phenothiazines, the tricyclic antidepressants, the benzodiazepines, phenylbutazone, erythromycin, chlorpropamide, methyltestosterone (dose dependent), and the oral contraceptives containing estrogens and progestins.

III. DRUG INTERACTIONS

Surveys in the United States have revealed the discomforting fact that patients on the average receive as many as 10 to 14 different medications during hospitalization. This regrettable trend toward unnecessary "polypharmacy" has greatly increased the likelihood of drug interactions and has become a new and important professional responsibility for the pharmacist, as well as the physician (47).

The number of documented adverse drug interactions is formidable. They should, however, be viewed in perspective. The prescribing physician needs to be aware of all serious drug interactions that may occur within the range of drugs prescribed. Many drug interactions, though of academic interest, may not be of sufficient clinical significance to justify withholding a drug's use. A number of drugs may offer therapeutic benefits in spite of adverse interactions with other medication.

No attempt will be made to list the major drug interactions. These are readily available in a large number of texts devoted to the subject. The general principles and typical samples of various types of drug interactions, however, which may be of interest in clinical drug research, are discussed below.

A. Mechanisms of Drug Interactions

The various factors that influence responses to single-drug therapy, including age, race, and physiologic and pathologic states, play an equally important role in drug interactions. The concurrent or close sequential administration of two or more drugs adds further dimension to the mechanisms of action and the possible outcome of the therapeutic program. Two or more drugs may (a) act independently, (b) interact directly with one another, or (c) interact indirectly with one another—one drug acting on an intermediate endogenous substrate that in turn modifies the effects of the other drug. Whichever mechanism is involved, the therapeutic effect of one or both drugs may be either increased (additive or synergistic) or decreased (antagonistic), and a new and unexpected adverse reaction may emerge. Drugs also may interact with other therapeutic devices or their containers, including disposable plastic syringes, rubber stoppers, and plastic bottles (48,49). This aspect of interaction is outside the scope and intent of this chapter.

B. Pharmacokinetic Pathways and Drug Interactions

Interactions may occur at one or more of the various states in the pharmacokinetic pathways of drugs in the body (i.e., during absorption, distribution, biotransformation [metabolism], sites of action, and excretion). Each of these states is considered separately.

1. Absorption

The extent and rate of absorption of drugs from the gastrointestinal tract is dependent on a number of factors such as bacterial flora, pH, motility, and the transport system involved in the absorptive process. Interaction of therapeutic agents in the gut may seriously impede absorption. Elevation of the pH of the stomach contents by antacids, for example, greatly delays absorption of acidic drugs such as aspirin and phenobarbital. Interaction of drugs forming poorly absorbed complexes, which occurs with tetracycline and antacids containing calcium, aluminum, and magnesium salts, may significantly decrease blood levels of the antibiotic (50).

2. Distribution-Competition for Transport Sites

The distribution of drugs is affected by the circulating plasma that transports them to sites of action, metabolism, and excretion. After absorption, most drugs are partially or almost totally bound to plasma and tissue proteins. The portion that is protein bound is pharmacologically inactive. It serves as a reservoir from which the usually much smaller unbound active fraction can be replenished as the free drug is metabolized and excreted (51).

When two drugs compete for a limited number of binding sites, the drug with the greater affinity for protein binding will displace a portion of the other drug. This increases the unbound active fraction of the other drug, thereby enhancing its pharmacologic effect. Sodium warfarin, for example, is about 98% bound to plasma protein and 2% free. If phenylbutazone, which has a greater affinity for protein binding, is given concurrently, it displaces warfarin from its binding sites. As a result, the bound portion of warfarin may drop to 96%, thereby increasing the active unbound fraction to 4%. Consequently, there is twice the amount of active warfarin available, and evidence of overdosage, such as spontaneous hemorrhage, may result (52).

It is evident that displacement of even small amounts of extensively protein-bound drugs can result in a relatively large increase in the active fraction. This commensurate rise in the therapeutic effect often leads to an undesirable or even dangerous level. Competition for protein-binding sites is an example of one drug acting on an intermediate endogenous substrate, thus affecting the activity of another medication.

3. *Interference with Drug Metabolism*

Biotransformation or metabolic inactivation of drugs occurs mainly in the liver and, to a lesser extent, in the plasma, kidney, and other tissues, depending on the enzyme system involved. In the liver, microsomal enzymes catalyze many of the metabolic processes involved in the biotransformation of drugs. These metabolic processes may involve nonsynthetic reactions such as oxidation, reduction, or hydrolysis, or synthetic reactions, including conjugation, whereby the drug is coupled with an endogenous substrate (53).

A number of different drugs, especially phenobarbital, have the capacity for enhancing synthesis and activity in the liver microsomes—a process known as enzyme induction. The increased amount of metabolizing enzymes induced by one drug results in the accelerated metabolism of a number of other drugs with metabolic inactivation pathways similar to that of the enzyme-inducing drug. Patients receiving phenobarbital, for example, metabolize coumarin anticoagulants, steroid hormones, antihistamines, analgesics, anti-inflammatory agents, diphenylhydantoin, and many hypnotic drugs at a greater-than-normal rate. They consequently experience diminished therapeutic activity and duration of action (54).

Some drugs, such as glutethimide, phenylbutazone, probenecid, and tolbutamide, stimulate only their own metabolizing enzymes. This may explain the increasing tolerance to these drugs that often develops after prolonged administration. On the other hand, there are drugs that can slow down or even arrest the metabolism of other drugs, resulting in their prolonged and intensified action, presumably by enzyme inhibition. Diphenylhydantoin intoxication, for example, may occur if either bishydroxycoumarin or isoniazid are given concurrently, as both the latter drugs inhibit the metabolic inactivation of the former. Also, allopurinol, a xanthine oxidase inhibitor, is used to reduce the synthesis of uric acid in gout. But xanthine oxidase is also the enzyme responsible for the deactivation of two potentially toxic antileukemic and immunosuppressant drugs, mercaptopurine and azathioprine. Concomitant medication with allopurinol will therefore elevate the plasma levels of these two cytostatic drugs and greatly increase the risk of serious bone marrow depression (55). More recently, cimetidine has been shown to inhibit the hepatic metabolism of theophylline, resulting in significant increases in serum concentrations of this drug (56). Cimetidine also interacts with, and produces significant increases in, the bioavailability of propranolol, oral anticoagulants, and diazepam, probably by the same mechanism (57–59).

4. *Modification of Drug Effect at Sites of Action*

Apart from drug interactions that result in increasing or decreasing the amount of drug available to the target organs, there are interactions that can directly or indirectly alter the response of the receptors in the target organs. A classic example of this type of interaction is the hypertensive crisis produced in patients concurrently receiving monoamine oxidase (MAO) inhibitors and an indirectly acting amine such as amphetamine or tyramine (found in cheese and fermented foods). The MAO inhibitors reduce the intraneuronal breakdown of norepinephrine, whereas the amines stimulate release of the excess of norepinephrine from the adrenergic neurons, thus inducing the crisis.

An altered response of one drug on its target organ may be affected by the action of a concurrently administered drug on another organ. The hypokalemia produced by potassium-wasting diuretics, for example, may potentiate the action of digitalis on the heart to the point of toxicity.

5. *Excretion*

The kidney is the prime organ for excretion of drugs. Drugs may be eliminated from the body either unchanged or as metabolites of the parent drug. Excretion of one drug through the kidney may be affected by concurrent administration of another and may result in an increased or reduced rate of excretion of either one or both drugs. This mechanism of action can be used to therapeutic advantage. The blood level of penicillin, for example, can be maintained at a higher level for longer periods by the concomitant administration of probenecid, which inhibits the penicillin transport system. On the other hand, quinidine reduces the renal clearance of digoxin. It also may displace digoxin from tissue-binding sites, increasing the serum level of digoxin and enhancing the risk of digoxin cardiotoxicity (60).

Drugs that alter the pH of urine can significantly affect the renal excretion of other drugs. Acid urine increases the effectiveness of mercurial diuretics. It also accelerates the excretion of basic drugs such as meperidine, tricyclic antidepressants, amphetamines, and antihistamines. Acidic drugs, such as aspirin, streptomycin, phenobarbital, sulfonamides, nalidixic acid, and nitrofurantoin have been shown to increase renal clearance in alkaline urine (61). The possible effects of urine pH on the renal excretion of drugs has been illustrated by the observation that if urine is rendered sufficiently alkaline, the excretion of amphetamine is markedly delayed and effective blood levels, after a single dose, can be maintained for several days (62).

C. The Beneficial Effects of Drug Interactions

It is customary, and indeed prudent, to emphasize the possible hazards of drug interactions. A number of drug interactions, however, with demonstrable beneficial therapeutic effects have been used to advantage in clinical practice for many years. Well-known examples of these include the chelating effects of calcium disodium edetate, dimercaprol, and penicillamine in chronic poisoning with arsenic, bismuth, gold, and lead, and penicillamine in chronic poisoning with arsenic, bismuth, gold, lead, and mercury; the simple expedient of alkalinization of the urine to increase renal elimination in poisonings with acidic drugs such as barbiturates and aspirin; the use of protamine sulfate to bind with heparin, forming an inactive complex, thus counteracting the effects of overheparinization; and the synergistic antibacterial effect of trimethoprim and sulfamethoxazole in the urine when these drugs are administered together.

Paradoxically, the unpleasant effects of a toxic metabolite produced by a drug interaction can have therapeutic benefits, such as the administration of disulfiram in the treatment of alcoholism. Furthermore, interactions at receptor sites to block the effects of a drug may be used to advantage (e.g., nalorphine in morphine poisoning). It is common practice to use antiparkinsonian drugs such as benztropine to ameliorate extrapyramidal symptoms—the commonly occurring adverse reactions to psychotropic drugs such as the phenothiazines, butyrophenones, and thioxanthenes. Combination therapy with the potassium-wasting diuretics and spironolactone (an aldosterone antagonist) or triamterene can be used to reduce excessive potassium loss and avert hypokalemia.

Whereas these and other beneficial drug interactions are well known and often used in clinical practice, some interactions that are currently considered to be adverse also may be applied therapeutically. For example, the analgesic effects of meperidine and the opiates are augmented by the concurrent administration of MAO inhibitors. This interaction can be used to increase the desirable effects of the analgesics without having to increase the dose. The regimen may have a place in the relief of severe chronic pain in patients with terminal malignant disease.

In spite of the well-known adverse reactions and dangers that attend the concomitant administration of many drugs, it is reassuring that the selective use of certain drug interactions has a positive place in pharmacotherapy; "sweet uses of adversity" as Hollister (63) has so aptly phrased it.

IV. COLLECTION, EVALUATION, AND REPORTING OF ADVERSE REACTIONS TO DRUGS

A. Collection of Adverse Events: Investigational Drugs

The adverse reaction potential of an investigational new drug, to some extent, may be indicated by its molecular structural similarities to other drugs of known actions and by pharmacologic and toxicologic preclinical studies in appropriate species of laboratory animals. The full adverse reaction profile of a drug, however, can only be determined by human experience and not until the drug has been administered to a relatively large number of patients of different ages, both sexes, and diverse ethnic groups, and for extended periods.

Phase 1, 2, and 3 clinical research programs required by the FDA and similar regulatory bodies in other countries are sufficient to define the more frequently occurring adverse reactions and to establish the safety of an investigational new drug. The safety evaluation during clinical drug development is not expected to characterize rare adverse events—for example, those occurring in less than 1 in 1,000 patients—but is expected to characterize and quantify the safety profile of a drug over a reasonable duration of time consistent with the intended long-term use of the drug. The number of patients treated for 6 months at dosage levels intended for clinical use should be adequate to characterize the pattern of ADEs over time. Usually from 300–600 patients should be adequate.

There is concern that, although they are likely to be uncommon, some ADEs may increase in frequency or severity with time, or that some serious ADEs may occur only after drug treatment for more than 6 months. Therefore, some patients should be treated with the drug for 12 months. In the absence of more information about the relationship of ADEs to treatment duration, selection of a specific number of patients to be monitored for 1 year is to a large extent a judgment based on the probability of detecting a given ADE frequency level and practical considerations. One hundred patients exposed for a minimum of 1 year is considered acceptable (64).

In response to a clinical trial in subjects with chronic hepatitis B infection, in which 5 of 15 subjects died of delayed hepatotoxicity after using fialuridine (FIAU), the FDA reviewed the requirements for the design of clinical trials, data analysis, and reporting. A task force recommended that a "worst-case" analysis be conducted in a semiannual report; a placebo control group should be included in early clinical trials when the underlying disease process is likely to produce AEs that might be confused with toxicity; the sponsor should estimate the expected incidence of death and serious AEs from the disease and should develop appropriate "stopping" rules; the length and type of follow-up period should be described to detect delayed toxicities; and the sponsor should develop safety monitoring and evaluation programs (65).

B. Collection of Adverse Events: Postmarketing

It is only by continued, close surveillance and tracking after a drug is available for general clinical administration under an expanded variety of circumstances that rare, sometimes severe, and even life-threatening adverse drug reactions or interactions are detected. Only then can the full adverse reaction spectrum of a drug be finally delineated. An example of a serious adverse reaction that was discovered postmarketing is the occurrence of serious regurgitant cardiac valvular disease during use of dexfenfluramine, an antiobesity drug, especially when the drug is used in combination with phentermine (FEN/PHEN). It should be noted that use of the combination was not approved by the FDA.

The FDA requires MAHs to submit PSURs to present the worldwide safety experience of a medicinal product at defined times after authorization. It is usual for MAHs to prepare CCDS containing CSSI. Most MAHs have developed SOPs for worldwide collection, analysis, and reporting of adverse events.

C. Methods for Obtaining Adverse Reaction Information from Patients

There are three generally accepted methods by which adverse reactions may be elicited from study patients:

1. Systematic questioning using a checklist containing the adverse reactions considered most likely to occur with the particular drug being studied.
2. Direct questioning without the use of a formal checklist. Questions concerning untoward symptoms should be put to patients in such a way that they do not, by suggestion, lead the subject into giving invalid information.
3. Recording only those adverse reactions that are volunteered by the patient or observed by the investigator or others involved in the study.

Of the three methods, the first, or checklist technique, has the greatest tendency to make patients introspective regarding their symptoms. Not surprisingly, this approach elicits the largest number of adverse reaction reports. Regardless of the method used, however, it is imperative that the questions be applied in the same way at each patient assessment, preferably by the same person, for the duration of the study. It is also recommended that patients be carefully questioned *prior* to administration of the study drug. It is remarkable how many so-called adverse reactions are, in fact, symptoms of other conditions present before the study treatment starts.

D. Reporting of Adverse Reactions

Drug safety and adverse reactions are closely related in an inversely proportional manner. In the United States, drug safety is under strict legislative control mandated by the FDA. Federal regulations require a sponsor to report adverse reactions for a drug product at both the investigational and the postmarketing stages.

1. Investigational Stage

A distinction should be made between an ADR and an AE. An AE is any untoward medical occurrence in a patient or clinical investigation subject who has been given a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product (1).

During the clinical investigation of a new drug (phases 1, 2, 3, and 4b) before FDA approval, it is the sponsor's responsibility to notify the FDA of all AEs as described in the chapter pertaining to the IND. The FDA has recently revised the regulations for expedited reporting of AEs and issued definitions of terms to comply with recent ICH Guidelines (66).

a. Serious ADE

A serious ADE is one that occurs at any dose that results in any of the following outcomes: death, a life-threatening ADE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious ADEs when, based upon appropriate medical judgment, they may jeopardize the patients or subjects and may require medical or surgical interventions to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

b. Life-Threatening ADE

This is defined as any ADE that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death).

c. Disability

This is defined as a substantial disruption of a person's ability to carry out normal life functions.

d. Associated with the Use of the Drug

There is a reasonable possibility that the experience may have been caused by the drug.

e. Unexpected ADE

An unexpected ADE is any reaction, the specificity or severity of which is not consistent with the current Investigator's Brochure, or, if an Investigator's Brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the Investigator's Brochure) rather than one that has not been anticipated from the pharmacologic properties of the pharmaceutical product.

When a serious adverse drug experience occurs, the investigator will provide the following information:

Subject identification number, age, and sex.

Duration of drug administration (includes dates of drug administration).

Dose administered (whether or not the code was broken in the case of a double-blind study) and route of administration.

Indication of drug (diagnosis for use).

Description of adverse event, including date and time of onset, as well as the date and time the event subsided. The outcome (recovered, alive with sequelae, dead) should also be stated. Any laboratory evaluations, ECGs, autopsy reports, etc., that are needed for understanding the adverse event should be submitted.

Concomitant medication, including the dose and dates of administration.

Current disease state, diagnosis, and medical history.

Dechallenge and rechallenge information.

Whether the subject was in imminent danger of death at the time of the adverse event.

Relationship to study drug. The investigator should state whether there was a reasonable possibility that the adverse event was caused by the drug/device.

Whether the adverse event was unexpected.

The investigator should complete and sign the appropriate form as required by the FDA. The FDA Medical Products Reporting Program (MedWatch) issued FDA Form 3500A for use by user facilities, distributors, and manufacturers for "mandatory" reporting of adverse events and product problems during the use of drugs, biologics, and devices. Form 3500 is for use by health care professionals and consumers for voluntary reporting. Adverse events associated with vaccines are reported to the FDA and the CDC using the VAERS.

If the ADE was not resolved at the time of the initial contact with the investigator, the investigational site will be contacted on a regular basis to determine the status of the subject until the ADE has resolved.

If the serious adverse experience is unexpected, fatal, or life-threatening and associated with the use of the drug, then the division of the FDA that has responsibility for review of the IND will be informed by telephone or facsimile transmission as soon as possible, and no later than 7 calendar days after, of the first knowledge of the event. The initial notification must be followed by a complete written IND Safety Report within 15 calendar days. All investigators involved in a multicenter study must be notified in writing within 15 calendar days. In addition, they, in turn, must apprise the individual governing IRBs of the report.

The FDA and all participating investigators will be notified in a written IND Safety Report of any adverse experience associated with use of the drug that is both serious and unexpected. Each notification must be made no later than 15 calendar days after receipt of the information.

2. *Postmarketing Stage*

Marketing authorization holders are required to develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing ADEs to the FDA. The definitions of postmarketing adverse experiences and unexpected adverse experiences are as follows (66):

a. Adverse Experience

An AE is any event associated with the use of a biological product in humans, whether or not considered product related, including the following: an AE occurring in the course of the use of a biological product in professional practice; an adverse event occurring from overdose of the product, whether accidental or intentional; an adverse event occurring from abuse of the product; an adverse event occurring from withdrawal of the product; and any failure of expected pharmacologic action.

b. Unexpected AE

An unexpected AE is any that is not listed in the current labeling for the biological product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity. "Unexpected," as used in this definition, refers to an adverse experience that has not been previously observed (i.e., included in the labeling) rather than one that has not been anticipated from the pharmacologic properties of the pharmaceutical product.

The definitions of a serious and life-threatening AE are the same definitions as used for investigational drugs.

Adverse drug experiences that are both serious and unexpected, whether foreign or domestic, must be reported to the FDA as soon as possible, but no later than 15 calendar days after initial receipt of the information (15-day Alert

Reports). Form 3500A or the CIOMS 1 form must be used for reporting. Additional information must be forwarded to the FDA in a follow-up report.

In addition, the frequency of reports of serious and unexpected AEs and reports of therapeutic failure must be reviewed periodically, and an increase in frequency must be reported to the FDA within 15 working days of determining the significant increase. Postmarketing periodic ADE reports are required at quarterly intervals for 3 years from the date of approval of the NDA and then at annual intervals.

E. Assessment of Adverse Reactions

The most difficult part of ADE reporting is the accurate assessment of the causal relationship of a drug to an alleged reaction. The likelihood that a drug contributes to, or is responsible for, an adverse reaction with any degree of certainty can be established only if adequate information is available.

The degrees of causal relationship between a drug and a suspected adverse reaction are defined as follows:

1. A remote causal relationship between a drug and an event exists when the temporal association is such that the drug would not have had any reasonable association with the observed event.
2. A possible causal relationship between a drug and event exists when the reaction (a) follows a reasonable temporal sequence from administration of the drug; (b) follows a known response pattern to the suspected drug; or (c) could have been produced by the patient's clinical state or other modes of therapy administered to the patient.
3. A probable causal relationship between a drug and event exists when the reaction (a) follows a known response pattern to the drug; (b) is confirmed by withdrawal of the drug; or (c) cannot be reasonably explained by the known characteristics of the patient's clinical state.
4. A definite causal relationship between a drug and event exists when the reaction (a) follows a reasonable temporal sequence from the time of drug administration or from the time the drug level has been established in body fluids or tissues; (b) follows a known response pattern to the suspected drug; or (c) is confirmed by improvement upon withdrawal of the drug (dechallenge) and reappearance of the ADR upon reintroduction of the suspect drug (rechallenge).

Accurate assessment of a causal relationship of a drug to an adverse reaction is beset with many difficulties. Most prominent among these are: (a) incomplete, time-related, drug-related information; (b) multiplicity of drugs administered in most cases; (c) lack of an objective means of demonstrating a direct relationship between a drug and an adverse reaction; and (d) the limited number of reaction patterns of the body to the entire range of physical, chemical, and biological causes of disease.

Because of these and other potential problems, the majority of drug-induced diseases fall into the "possible" category. Very few can unequivocally be labeled as definite.

V. SUMMARY

The main objective of all adverse reaction reporting programs continues to be the collection of data sufficient to evaluate, in a meaningful way, the benefit-to-risk ratio of new drugs. In this way, significant drug hazards may be detected and corrective measures implemented at an early stage. In extreme cases, this may even involve total withdrawal of the drug from further clinical investigation or, in the case of approved drugs, from general clinical use. Whereas a number of official regulations governing clinical research may seem to be overly restrictive at times, the overall concern for proven safety and established efficacy of new drugs cannot be questioned. All new drug development efforts must be supported by scientific presentation of accurate data and the continuing recognition of the rights of all patients participating in clinical drug studies.

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10

Institutional Review Board/ Independent Ethics Committee and Informed Consent: Protecting Subjects Throughout the Clinical Research Process

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I. INTRODUCTION

The United States Food and Drug Administration (FDA) statutes that are published in Title 21 of the Code of Federal Regulations (21 CFR) identify and define the activities involved in the clinical research process. These codified regulations are designed to protect the rights, safety, and welfare of subjects of clinical investigations. An amendment to Title 21, dated July 27, 1981, specifically required that the conduct of clinical investigations would include: (a) obtaining informed consent of all subjects, and (b) approval of all research proposals by Institutional Review Boards (IRBs).

More recently, the Department of Health and Human Services (DHHS), FDA, printed the guideline entitled "Good Clinical Practice: Consolidated Guideline," in the Federal Register, which underscored the importance of these and other regulated activities. Although the guideline is not perceived by the FDA as a substitute for the codified regulations, the FDA's recognition of this guideline is evidenced by a statement noting it as representative of the Agency's current thinking on GCPs. The significance of the guideline, "The International Conference (ICH) on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use," is that it supports the concept and implementation of a unified standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects in clinical investigations in the United States, Japan, and the European Union. Informed consent and IRB activities are discussed throughout the document to address how studies are conducted.

II. BACKGROUND

The National Research Act passed by Congress on July 12, 1974 mandated the establishment of IRBs, which for the first time, formalized the review of federally funded research. Also, this act provided for a National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and resulted in the publication of The Belmont Report in 1979. Although the Belmont Report was never officially adopted by Congress, it provided a fundamental guideline for the protection of human subjects in research.

Historically, private practitioners conducting clinical research were exempt from the IRB and informed consent regulations required of institutional, that is, university or hospital researchers. The amended regulations on July 27, 1981, requiring IRB review and approval of all research, increased the need to establish IRBs that would review and approve research proposals that might not be affiliated with a major research center, teaching hospital, or university. In the current regulatory environment, all NDAs submitted to the FDA in support of all drugs, biologics, or medical devices require proof that IRB approval was obtained before implementation of the research. Evidence of continuing review by the IRB throughout the trial must also be demonstrated. The only exemptions from IRB review are investigations that started before July 27, 1981 and that fit categorical descriptions defined in the regulations.

III. INSTITUTIONAL REVIEW BOARD DUTIES

The goal of the IRB (known also as the Independent Ethics Committee, or IEC) is the protection of the rights, safety, and welfare of human subjects involved in clinical research investigations. The review board is, therefore, primarily responsible for the evaluation of the proposed research. All evaluations should have the following objectives: (a) to determine that the research is properly designed; (b) to determine that the benefit of the intended therapy will outweigh the potential risk; and (c) to determine that the patient will be provided with adequate information to enable him or her to make an informed decision regarding participation in the clinical trial.

If the benefits do not sufficiently outweigh the risks, the IRB may either refuse to award approval of the project/study protocol or require a modification to research that limits the risk/benefit ratio by approving it for a more defined or limited patient population.

Because IRB review/approval and continuing review processes are required for all clinical investigations performed in support of a research application or a marketing permit for FDA regulated products, it is important to assure that projects are not initiated before these approvals are obtained.

It is also important to note that, although IRBs are subject to codified regulations stipulating their functions and responsibilities, other key players in the clinical research process are intrinsically involved in review processes to ensure the protection of subjects' rights. Specifically, clinical investigators are bound by 21 CFR 312.66 (Assurance of IRB review) to obtain initial and continuing approval reviews, to report changes in research activity, to report unanticipated problems relating to risks to subjects, and to provide study status. In addition, sponsors of clinical trials are bound by 21 CFR 312.53 (Selecting investigators and monitors) to inform the IRB, albeit through the investigator, of these obligations. The sponsor secures the investigator's agreement to fulfill these obligations by obtaining a signed and dated Investigator's Statement before initiating a trial.

IV. INSTITUTIONAL REVIEW BOARD MEMBERSHIP AND RESPONSIBILITIES

The composition of an IRB membership is specifically defined by the FDA in 21 CFR Part 56 and must include the following basic requirements, which must be adhered to:

1. Members of both sexes at each meeting.
2. Scientific (e.g., physician, research scientist) and nonscientific (lawyers, clergy) members; a minimum of one nonscientific member at each meeting.
3. A minimum of one member who is unaffiliated with the institution at each meeting.
4. No member with a conflict of interest.
5. A minimum of five voting members at each meeting.

Some IRBs have expanded their working policies or standard operating procedures to include the following additional requirements:

1. One member representing cultural or ethnic diversity.
2. One member representing a special interest group, if applicable (e.g., handicapped).

3. The considerations of socioeconomic factors and local attitudes.
4. Financial considerations impacting subjects.

Because there are some IRBs with a large membership and all members may not attend every meeting, it is imperative that the basic requirements for constituting an IRB be met by all present and voting members. A standard roster or an IRB membership list should be maintained, which lists the alternative members and indicates that they have equal professional status and meet the basic qualifications.

All IRBs are ultimately responsible for the unbiased determination of whether a proposal for clinical research is acceptable in terms of the standards of professional practice, the institution or individual undertaking the research, and the patient population. Therefore, proposals considered for approval at convened meetings must receive approval by the majority of the members present at that meeting.

If a voting member has a conflicting interest in the review, for example, a member who will be directly involved in the proposal being reviewed for approval, that individual may provide information but must abstain from voting. In addition, individuals with expertise in a specialized area may be invited to assist in reviews at a meeting; however, these individuals will not be permitted to vote.

V. IRB DOCUMENTATION AND OPERATIONS

Institutional review boards must maintain written procedures of all operations. All activities associated with the following operations must be recorded:

1. Conducting initial review and continuing review/approval of research.
2. Conducting expedited review/approval of research.
3. Ensuring that changes in research activity are reported.
4. Ensuring that changes in previously approved research are not implemented without review and approval.
5. Reporting of serious risks.
6. Reporting of significant findings.

All IRBs are required to maintain records (minutes) of meetings and documents for at least three (3) years after completion of a study. In addition, IRBs are responsible for reporting investigator noncompliance to their institutions, sponsors of clinical research, and the FDA. It is important to note that IRBs have the regulatory authority to suspend or terminate research they previously approved if the research ceases to be conducted in accordance with the IRB's requirements. Research that has been associated with unexpected or serious harm to research subjects may be suspended or terminated.

VI. INFORMATION REQUIRED FOR IRB REVIEW

All information submitted to an IRB for review of a research protocol is provided by the clinical investigator seeking approval to conduct the research. The standard documents typically provided are the research protocol, a sample of the intended informed consent, and the Investigator's Brochure or package insert. It has become common practice recently to provide patient information sheets or instruction guides as well, advertising that will be used to recruit subjects, and any scheduled reimbursements to compensate patients for their time or expenses incurred during participation in a trial. Although the regulations do not require these additional documents, FDA Information Sheets suggesting that they be provided have served as guidelines or references for common practices that facilitate regulated activities. The regulations require that the Investigator's Brochure be submitted for studies conducted under an investigational new drug application in the section defining IND content and format (21 CFR 312.23(a)[5]) and in the section regarding informing investigators (21 CFR 312.55[a]). In the ICH GCP Consolidated Guideline, it is specifically stated that certain documents be obtained for review, as part of the responsibility of the IRB/IEC (Sec. 3.1. Responsibilities, 3.1.2).

The review of the protocol ensures that there are adequate selection criteria and procedures to protect vulnerable study populations. In addition, information within the protocol, the informed consent, and the Investigator's Brochure are reviewed to assess safety information that may affect subjects. Institutional review boards are empowered with the authority to approve or disapprove research activities that are covered by regulations, as well as to require modifications to secure approval. Informed consents will be reviewed to assure that all the information provided is in accordance with 21 CFR 50.25; the IRB may also require that additional information be provided to study subjects in a separate format, such as a patient information sheet. If this requirement is waived, a written statement may be given to the subject. If a very short "window of opportunity" exists to dispense a research treatment to avoid a devastating or fatal outcome, a waiver for this requirement may be requested. It is important to note, however, that the sponsor must clearly describe or define the situations that would require testing without administering a written informed consent. Also, provisions that will be made to obtain the consent from family members must be in place. This issue will be discussed in more detail in the section on informed consent. In summary, the following criteria are used by IRBs to approve research:

1. Minimal risk
2. Risk/benefit ratio
3. Equitable patient population

4. Informed consent documentation
5. Planned study management/monitoring
6. Patient privacy and confidentiality
7. Rights and welfare of a vulnerable population

The FDA does not prohibit the use of advertising. However, because it has become a popular tool for increasing the enrollment rate of subjects in clinical studies, the FDA Information Sheet, entitled "Advertising for Study Subjects," was created to serve as a guideline. This guideline recognizes advertisements as an extension of the informed consent and subject selection process and defines them as a research activity and subject to review, primarily to protect subjects from misleading advertisements. Because advertisements are perceived as a research activity, they should be submitted for review and approval, although the regulations do not specifically require a review.

The FDA Information Sheet notes what the contents of advertisements should be, as follows:

1. The name and address of the clinical investigator
2. The purpose of the research
3. A summary of criteria used to establish eligibility
4. A description of the benefits (e.g., no-cost health examination)
5. Time or other commitment from the subject
6. The location of the research and the person to contact for further information

Sample advertising submitted to the IRB may be in various media format. Whether the advertisement is in the form of newspaper advertisements, posters, brochures, leaflets, radio or television advertisements, and even notices posted on the Internet, they are all subject to the same requirements noted above. All copy, including audio or video scripts or videotape, should be submitted for review and approval before use. All of the requirements for written copy apply to all advertising modes.

The IRB must ensure that advertising does not include misleading information or statements implying that the drug or device is safe or effective for the indication being investigated, or that the drug or device is equivalent or superior to any other drug or device. In addition to misleading potential subjects, statements that could be considered to be promotional claims would be in violation of statutes regulating the promotion of investigational drugs or devices.

The issue of subject reimbursement also has to be considered by the IRB to ensure that subjects are not induced to participate in a study because of excessive payments, but rather are remunerated adequately for their time and inconvenience. If a subject participates in a study involving more than one study visit, the amount of reimbursement per visit should be stated. Visits that require additional time or cause inconvenience to the subject and have higher remunerations should be stated when applicable. Conversely, it should be stated if there are visits for which no reimbursement is scheduled. Finally, subjects should be informed if there is a caveat that, if the study is not completed, a prorated amount will be reimbursed, rather than the total amount indicated for study completion. All of these items should be delineated in the informed consent.

Informed consents, which must be signed by subjects before they participate in a study, reflect payments that will be made and, as mentioned, should include how they will be scheduled. The review of this information falls under the purview of IRB responsibility for two reasons. First, payment is perceived as a benefit, and it is the IRB's responsibility to determine that the benefit does not reflect an unduly coercive amount that may persuade individuals to participate in a study they ordinarily would not consider. Second, the IRB is also responsible for evaluating the investigator's responsibilities regarding the submission of this document.

VII. INITIAL APPROVAL AND CONTINUING REVIEW

The critical documents required for approval of research, that is, protocol, informed consent, and Investigator's Brochure, are usually presented to an IRB chairperson by the principal investigator. Copies of the pertinent documents are supplied to the IRB members for thorough review before they vote on the proposed research project. Any and all elements of the project may be deliberated and may result in recommendations to modify any part of the research.

Clinical investigators will be notified, in writing, of all IRB decisions regarding the approval/disapproval of research or modifications to the research required to obtain approval. Approvals will identify the study and include the date of approval and the IRB chairperson's signature. If a decision to disapprove a research proposal is made, the notification will include the reasons, to provide the investigator with an opportunity to respond in person or in writing. All written documentation between the IRB and the clinical investigator should be accompanied by a transmittal letter to ensure verification after any action or decision. All correspondence should be date-stamped upon receipt, and all study documentation should be stamped with the date of IRB approval. In addition, documentation submitted to the clinical investigator (and the IRB) should be dated to distinguish between final documents and draft versions to avoid accidental approval of a draft document.

Regulations regarding the IRB review of research require the review of protocols at least once per year; however, the intervals are based on the degree of risk to the subject and are usually specified by the IRB at the time of initial approval. Finally, IRBs have the authority to observe, or designate a third party to observe, the consent process and the research.

VIII. EXPEDITED REVIEWS

Expedited reviews are used by IRBs to review and approve minor changes in previously approved research, either because the change is administrative in nature or because the research (or change in the research) involves no more than minimal risk to the subject. This procedure requires review only by the IRB chairperson, or by one or more reviewers designated by the chairperson who are voting members of the IRB. In addition, when and if the expedited procedure is invoked, every member must be advised of all approvals made through this procedure. It is important to note that expedited review procedures are used only under the limited circumstances addressed above and do not replace a full IRB review of research proposals. The original documentation of all IRB reviews and decisions should be maintained by the principal investigator; copies should be maintained by a trial's sponsor.

IX. THE INFORMED CONSENT FORM

Overall, the informed consent regulations (21 CFR Part 50) apply to all clinical investigations regulated by FDA, including clinical investigations that support applications for research or marketing permits for products the FDA regulates. The general requirements for informed consent are discussed below.

As mentioned earlier, the clinical investigator is ultimately responsible for assuring that a subject in a clinical investigation is fully informed of the project and apprised of the procedures to be followed and the risks and benefits of the therapeutic regimen proposed in the research. The informed consent process requires that a written consent be obtained from each patient (or his legally authorized representative) to verify that the above-referenced obligations have been satisfied. On November 5, 1996, the FDA published a final rule—in fact a change to an existing regulation—requiring that a consent form signed by the subject or the subject's legally authorized representative be dated by the subject (or legally authorized representative) at the same time it is signed. This ruling became effective on December 5, 1996, enforcing by regulation an element of GCP that has been implemented routinely by clinical researchers in recent years. In addition, the FDA amended the regulation regarding case histories (21 CFR 312.62) (a) to specify that these must document that informed consent was obtained before a subject participated in a study, and (b) to clarify what should be included in a case history.

The IRB's oversight responsibility is highlighted by this amendment, which was enacted to ensure that an informed consent is obtained before any trial-related clinical procedures are performed.

During the informed consent process, clinical investigators should plan to allow sufficient time for patients to review a consent and ask questions regarding the research. Patients must be permitted to take the form with them while they are considering participation; however, the form must be signed in front of a witness. In addition, the IRB may request that a witness sign the informed consent, as well. The principal investigator may not serve as a witness. A copy of the consent document must be provided to the patient.

Informed consents should be written so that they can be understood by a layperson. In general, the overall document should not contain words or explanations that could not ordinarily be understood by an individual who has completed an eighth-grade level of education. All technical, medical, or legal terminology should be explained to a prospective subject. Patients unable to read English should have the informed consent made available in their native language. The translation of the informed consent should be documented as being completed by a qualified individual. It is recommended that translations be used only in instances where a significant amount of the proposed study population would require a translation.

Finally, informed consents should not contain any coercive language that unfairly persuades or influences a subject's decision to participate. The consent should not contain exculpatory language that either requires, or appears to require, a subject to waive any legal rights or releases or appears to release an investigator, sponsor, institution, or any other agent of a clinical investigation from liability for negligence. The moral and legal ramifications of this type of language are obvious.

Aside from the general requirements for informed consent that have been discussed, some basic elements must be included in all informed consents. Additional elements are to be included only when they are deemed appropriate.

A. Basic Elements of the Informed Consent (21 CFR 50.25)

1. A statement that the study involves research, an explanation of the purposes of the research, and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
2. A description of any reasonably foreseeable risks or discomforts to the subject.
3. A description of any benefits to the subject or to others which may reasonably be expected from the research.

4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that may be advantageous to the subject.
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.
6. For research involving more than minimal risk, an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

B. Additional Elements of the Informed Consent (21 CFR 50.25(b))

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
3. Any additional costs to the subject that may result from participation in the research.
4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
5. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
6. The approximate number of subjects involved in the study.

All consent documents and the entire informed consent process should be designed and implemented to be in compliance with the above-stated regulations, as well as consistent with the principles of the Declaration of Helsinki, World Medical Assembly, Revised 1996, 48th General Assembly, the accepted basis for clinical trial ethics incorporated into the ICH GCP Consolidated Guideline.

The ICH GCP Consolidated Guideline encompasses the procedures involved in the administration of the informed consent process that are included in the US CFR. However, it is worth noting that, in addition to expanded explanations for some of the basic and additional elements of informed consent in the regulation, other items are included.

The guideline's descriptions of the procedures also require that the probability for random assignment for each treatment be included in the discussion. Also, the guideline explicitly states that invasive procedures must be explained when they are part of the treatment. Furthermore, the guideline states that if there are anticipated prorated payments to the subject for participating in the trial, the subject should be informed via the consent form. This is somewhat of a departure from the United States' regulations, which do not require that this information be stated in the informed consent. However, the FDA Information Sheets state that payments should not be contingent on study completion and that the proposed schedule should be evaluated by the IRB to determine that payments are reasonable and do not unduly influence a patient to remain in a trial. Because payments are perceived as a benefit, it is suggested that the outline of the payment schedule and the conditions determining the payments be specified in the informed consent.

The guideline specifically states that an explanation of the subject's responsibilities must be referenced during the informed consent discussion and included in the consent form and any other written information. Also, the person responsible for conducting the informed consent discussion is required to sign and date the informed consent. The document must specify the parties granted direct access to the patient's original medical records.

The importance of a correctly documented informed consent and an adequately implemented consent procedure cannot be stressed enough. Beside understanding these requirements, one should be equally mindful that there are situations that may deviate from the norm, but require equal attention. This includes the necessity of resubmitting an informed consent and obtaining reapproval from an IRB when a consent has been significantly revised or altered, usually because of a protocol amendment. A full explanation of the revisions and any associated changes in the study procedures should be provided to each subject who signed the original consent form, and he/she must be required to re-sign a revised form before any changes in the research are performed. All revised forms must be submitted to the IRB for review and approval. If, during the course of a trial, an informed consent was signed by a legally authorized representative because a subject was either incompetent or a minor, the consent should be readministered to obtain the signed/dated signature of the patient who regained competency or reached the age of majority, respectively.

Although the age of majority in most states is 18 years, approximately ten (10) states permit higher or lower consent ages. Also, some local/state laws permit consent at lower ages, depending on various circumstances, such as abortion; prevention, treatment, or diagnosis of a sexually transmitted disease (STD); pregnancy; and drug or alcohol abuse.

C. Oral Consent

A "short form" written consent document, stating that the elements of informed consent required by 21 CFR 50.25 have been presented orally to the subject or the subject's legally authorized representative, is included in the regulations. However, clinical investigators do not recognize oral consent as a practical or appropriate alternative to obtaining documented informed consent whenever possible. The following requirements are necessary when the use of a short form informed consent is implemented:

1. A witness to the oral presentation must be present.
2. The IRB must approve a written summary of what will be said to the subject/representative.
3. The short form is to be signed by the subject/representative.
4. The short form and summary will be signed by the witness.
5. The person administering the consent will sign a copy of the summary.
6. Copies of the short form and the summary will be given to the subject/representative.

Any research conducted in the United States must comply with the federal regulations regarding informed consent, despite the type of form or procedure used. It is important for those involved in patient safety and welfare issues to know that there are some state or local laws that may have additional requirements regarding informed consent procedures. The California Research Subjects' Bill of Rights is an example of a state law in California that requires all research subjects to be provided with a document entitled "Experimental Subjects Bill of Rights" before they participate in a research trial.

X. EMERGENCY USE OF INVESTIGATIONAL DRUGS/BIOLOGICS

The regulations include a provision for the emergency use of an investigational drug or biologic when a human subject is (a) in a life-threatening situation in which no standard acceptable treatment is available and (b) there is not enough time to obtain IRB approval (21 CFR 56.102).

When a human subject does not meet the criteria stipulated in an existing study protocol or if an approved study protocol is not available, the manufacturer of the test article should be contacted to determine if the company will make the test article available for emergency use under the manufacturer's IND. If an emergency occurs before an IND submission and the manufacturer agrees to make the test article available, the FDA would have to authorize shipment.

The specific regulation (21 CFR 56.104) is actually an exemption from prior review and approval by the IRB; however, it can be used only when the specific conditions described in 21 CFR 56.102 are met, and it allows for only one emergency use of the investigational product. The investigator must file a report of its use within five (5) days to comply with the exemption regulation. Also, some institutions require IRB notification before the emergency use. Finally, the manufacturer may require an emergency use approval letter or at least a written statement that the IRB has been informed of the emergency use and acknowledges that the requirements stipulated in the exemption regulation have been met. All subsequent uses of an unapproved test article are subject to usual IRB review and approval procedures.

A. Informed Consent During Emergency Use

In an emergency use situation in which an investigator has determined that there is insufficient time to obtain informed consent from a subject or legally authorized representative, the investigator is required to have the determination reviewed by a physician who is not participating in the clinical investigation and to obtain a written certification of the following informed consent requirements (21 CFR 50.23) before use:

1. The subject is confronted by a life-threatening situation necessitating the use of the test article.
2. Informed consent cannot be obtained because of an inability to communicate with the subject or to obtain legally effective consent from the subject.
3. There is insufficient time to obtain consent from the subject's legal representative.
4. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

Although it is best that both the investigator and a physician independent of the clinical trial determine the necessity for emergency use of an investigational product prior to its use, if this is not possible, the investigator must have the determination of use reviewed, evaluated, and submitted to the IRB within five (5) working days after use of the test article.

XI. ASSURING THAT REGULATORY OBLIGATIONS ARE ADEQUATELY IMPLEMENTED

The complexity of clinical research is evidenced by the associated regulatory and clinical documentation required before an IND is filed, throughout the clinical trial process, and ultimately, during the preparation of an NDA filing. A sponsor must ensure that the studies supporting an NDA contain quality data that substantiate claims of safety and efficacy. This process is facilitated when a sponsor evaluates the acceptability of the regulatory obligations and responsibilities required by investigators and sponsors. Thus, the ultimate concern regarding the safety and efficacy claims stated in a submission can be assessed. Although this chapter does not address the auditing and inspection techniques used to identify potential deficiencies, it is important to understand why these regulations have been established, the type of deficiencies that are identified, and the impact of poorly implemented GCPs.

In 1986, the preamble to the IND Rewrite stated that the detail of an inspection may be based on the knowledge that a sponsor has audited subject records. The preamble further reiterated that "FDA's policy to audit two or more critical studies will continue." These statements regarding FDA's inspection efforts, as well as the FDA Statement of Enforcement Policy (1990) and recent activities promulgated through the Office of Criminal Investigations, has encouraged sponsors of clinical trials to establish and implement quality assurance departments and programs. Internal clinical quality assurance departments have developed standardized procedures to provide objective, independent assessments of processes that will assure upper management that trials are being conducted according to GCP procedures, including patient protection, safety, and welfare to produce accurate and reliable data. In addition, tools to identify and oversee corrective actions facilitate the speed and quality of submissions and provide opportunities for training in monitoring and the continuing improvement of standard operating procedures used in the oversight of clinical research. The ability to identify, correct, and prevent inadequacies that could result in disciplinary regulatory actions or, in the worst case, delay or prevent an approval, underscores the benefit of this proactive approach. Optimally, quality assurance personnel can facilitate the inspection process by helping to identify the appropriate staff in the functional area being inspected. Furthermore, a quality assurance presence can be helpful in advising personnel regarding study documents that are provided to the FDA, providing a scribe to generate minutes, facilitating daily debriefing meetings, and advising management of inspection findings and corrective actions. The importance of the IRB and IC regulations has also been highlighted by FDA's recognition of the ICH Good Clinical Practice Guideline, which underscores these elements in the regulations.

XII. AUDITS VERSUS INSPECTIONS

The focus of both audits and inspections is to review clinical research-related activities and associated documentation, to determine the adequacy of the conduction of the activities, and to determine the accuracy and reliability of the data reported. Clinical research nomenclature commonly refers to audits as internally generated processes and inspections as official reviews by a government authority, such as the FDA. Both audits and inspections are actually assessments of the clinical research process and share the goal of identifying deficiencies for corrective action. The essential difference is that an audit initiated as an independent review by a company is often conducted proactively to identify and correct inadequate procedures or to verify the accuracy and reliability of data being collected for submission. Inspections are routinely conducted by regulatory authorities to protect the public safety and welfare, as well as to respond to potentially illegal or inappropriate research activities that have been exposed. Regulatory authorities can also impose punitive actions or pursue legal sanctions to promote correction of inadequate or illegal clinical research activities.

Irrespective of whether audits are initiated by the IRB, a sponsor, or the FDA, a number of commonly identified deficiencies have been noted and are addressed below. It is important to note that investigational sites, sponsors, and IRBs are all subject to FDA-issued warning letters or repeat inspections to verify that deficiencies have been adequately corrected.

A. Common Auditing/Inspectional Findings: IRBs

Clinical investigators routinely submit protocols and informed consent documents to IRBs to obtain an independent evaluation of the risk/benefit ratio of a study in order to meet their obligation to protect patients' safety and welfare. The Institutional Review Branch of the FDA's Division of Scientific Investigations conducts inspections of the IRBs that review and approve investigational studies for biologics, drugs, medical devices, and food additives. Although the regulations specifically outline the IRB requirements and responsibilities in this review process, inspectional findings from routine surveillance, as well as directed inspections, have revealed seven commonly cited deficiencies that have resulted in regulatory or administrative actions:

1. A lack of sufficiently documented standard operating procedures describing an IRB's procedural responsibilities and activities.
2. Meeting minutes that do not fully detail actions taken or voting conducted at a meeting. Examples of insufficiently documented minutes may include inadequate reporting of voting on protocols or amend-

ments to protocols, the basis for disapproving a protocol, or summaries of relevant discussions or issues.

3. Documentation that is not available to verify that a quorum was present at convened meetings to review proposed research and that a majority of those members present at the meeting approved the proposal.
4. Lack of documentation to verify that the IRB provided continuing review of research activities that it initially approved at intervals of no less than one (1) year, but appropriate to the level of risk to the subject.
5. IRB membership lists or rosters that are not consistent with the elements required in 21 CFR Part 56. (See section entitled "Institutional Review Board Membership and Responsibilities".)
6. Institutional review board records that do not adequately track or log research documents that have been submitted by the clinical investigator, including protocols, amendments, consent forms, Investigator Brochures, IND safety reports, advertisements, patient information sheets, and correspondence between the investigator and the IRB.
7. A lack of approval notifications, approval notifications that do not adequately identify the research document (or the version of the research document) that has been approved, or missing dates of approvals.

B. Common Auditing/Inspectional Findings: ICDs

Informed consent issues rank among the most commonly cited deficiencies reported by FDA inspectors. Findings can include deficiencies in the content of the informed consent, as well as the actual informed consent administration process. Most frequently noted are the following inadequacies:

1. All the basic elements of the informed consent (according to 21 CFR 50.25) are not included.
2. The content of the informed consent is inadequate.
3. Institutional review board approval of the consent or revised consent(s) has not been obtained.
4. The informed consent has not been properly administered to the subject of the clinical investigation or a legal guardian.

To limit inspectional findings related to informed consent deficiencies, auditor reviews of informed consents can be conducted proactively, that is, before being submitted to IRBs for review and approval. Inadequacies regarding the lack of required content, the use of technical rather than lay language, readability above an eighth-grade level, and consents that are culturally and linguistically inappropriate for the anticipated population, are examples of problem areas that are frequently overlooked. Also, it is important to assure that subjects of clinical trials are provided with the most recent version of an IRB-approved informed consent. It is recommended that informed consents include the version number, date, and page number on the bottom of each page of the consent form, which has been either signed or initialed and dated. Along with a correctly signed/dated informed consent, it is often beneficial to provide patient information sheets or subject instruction sheets to clarify or reiterate the study procedures.

In conclusion, once the regulatory compliance issues regarding informed consent have been satisfied, it is essential to ascertain the subject's comprehension of the informed consent. Documentation of the administration and comprehension of the informed consent by the subject should be a routine component of the process.

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Statistical and Data Management: Collaboration in Clinical Research

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I. INTRODUCTION

This chapter discusses the role of statisticians and data management personnel in clinical protocol design, execution, and analysis. Although the uninitiated might imagine that statisticians arrive on the scene after all of the data from a trial have been collected and are waiting to be "crunched," statistical departments spend most of their time working throughout the trial to make sure that each patient visit has been recorded completely and with information that is internally consistent.

The quality checking for which statisticians and data management personnel are responsible includes many types of review and analysis for accuracy, completeness, and validity. It is useful to bear in mind in this age of multicenter trials involving thousands of patients examined over a period of years that even a very small trial may generate a considerable amount of data. If a study enrolls only 25 patients who visit the clinic only four times, each patient visit may generate as many as 60 to 100 variables, resulting in a total database of 6,000 to 10,000 pieces of data. If these tidbits of information are not accurate recordings of valid findings, the whole trial could prove worthless.

In addition to being accurate and valid, clinical findings must also be relevant to the anticipated therapeutic effect. They must be sufficient to prove that the efficacy of the study drug is comparable to, or perhaps greater than, a well-chosen and well-blinded control, and that its *safety* has been similarly profiled. Obviously, if the study design and protocol, including such basics as the study sample size, are not adequate for this complex task, the data collection and number crunching could be carried out at great expense, but with little to show for it. Thus, the expertise of statisticians is much needed in the planning stage of any clinical investigation.

Even before work begins on designing a trial for the first use of a new compound in human subjects (phase 1), statisticians play a crucial role. The data derived from animal studies must be thoroughly analyzed. There must be justification of the probable safety and usefulness for the experimental use of this new drug in healthy individuals or, if warranted, in suitable patients.

When helping to make the "go" or "no go" decisions and to select quantifiable variables for the research protocol, the statistician is truly a collaborator in clinical research and continues to do so while carrying out the role of data analyst. However, beyond these important collaborative efforts, the statistician performs yet another crucial role in the clinical research of drugs and devices.

The methods of quantification and statistical manipulation must be acceptable to the FDA, whether the product application at issue pertains to investigational use of a new compound or device, or to marketing. The essential fibers of any application to FDA are the set of premises and assumptions, the methods of protecting the integrity of these premises and assumptions, and the selection and design of quantifiable variables and the formulas for their statistical analysis. Together, they must comprise a theoretical construct acceptable to the FDA; otherwise the analyses will be rejected by the FDA. Then the data will have to be resorted and reanalyzed according to other statistical theorems, which may require clinical data not originally collected—a devastating consequence to face after years of hard work.

This is why the clinical research team relies on statisticians, who can review the clinical and statistical assumptions at early and intermediate stages of the investigation. The province of the statistician encompasses the decision to perform the study, study design, patient sample size and population characteristics, study execution, and data recording, collection, analysis, and interpretation. Data management personnel coordinate the data recording and collection activities. The statistician's ability to direct the redesign of a protocol before the clinical work begins represents an invaluable aspect of his or her work. This chapter will therefore provide statisticians with suggestions about the type of contribution to be made in collaboration with other team members at each stage of clinical investigation, beginning with analysis of the preclinical trials. Although a review of some basics is included, this chapter is not intended to be a complete course in statistics. The role of data management will also be mentioned where appropriate.

II. THE FDA GUIDELINES

Throughout the years of product development, the statistician's contributions will come closest to the mark if it is borne in mind that the objective is to convince

FDA officials of safety and efficacy by using the methods that FDA statisticians and other experts have agreed are appropriate. The analyses and presentation of data will be most convincing if performed in accordance with the FDA's "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications" (3) and with the particular requirements of the clinical and statistical reviewers assigned to the particular drug at issue. In certain instances, it may happen that new statistical methods, which the statistician believes to be state-of-the-art, powerful, and appropriate, are not those embraced by FDA reviewers. Many of these reviewers are not statisticians, but rather experts in chemistry or clinical medicine who are uncomfortable with less well-known statistical methods. The right choice of statistical method in such cases is, of course, the method that is appropriate and will be found acceptable and convincing. Such choices must be made as early in the planning of the investigation as possible. Periodic discussions with FDA statisticians and other appropriate FDA staff, such as end of phase 2 and pre-NDA meetings, should be arranged.

This chapter will attempt to elucidate the roles of statisticians and how these roles affect the overall teamwork needed to guide a new drug successfully through investigational work and to market. This chapter is not intended to provide instruction on basic or evolving statistical methods or concepts. For this kind of background information, the reader will find sources referenced in the bibliography at the end of the chapter (1,2,4).

III. THE FIRST CLINICAL TRIALS

The IND application allows the FDA to determine whether it is probably safe to administer a particular drug product to humans and whether the anticipated specified therapeutic action is likely to outweigh anticipated adverse reactions. Probability and "likelihood" are the province of the statistician. It is not possible for statistical manipulations of recorded events to prove absolutely that any predicted event will actually occur. Statistics can provide an estimation of the likelihood that a particular treatment previously administered in a particular dosage form at a particular level will continue to yield similar therapeutic effects and side effects in a similar population.

When the major transition from an animal population to human subjects is proposed, the statistical probabilities derived by the statistician must be discussed by experts familiar with the similarities and differences between human organ systems and cell surface receptors and those of the laboratory animals. Thus, the extrapolations in the IND from the preclinical work in animals to the probable effects in humans rest on a combination of statistical inferences and comparative assessments by experts in pharmacology, toxicology, pathology, and biochemistry. Their expertise, in turn, rests to some extent on the statistical findings of previous comparisons between human and animal handling of similar pharmacologic compounds.

The application of probability theory makes it possible to proceed on the basis of incomplete knowledge. However, the extrapolations must be as precise as possible. The IND does not propose a blanket approval of the administration of the new drug in any form at any dose to any number of sick or healthy people simply because it happened that none, or very few, of the laboratory animals died. Instead, the IND proposes specific doses, a specific regimen over a named period in a human population of a size determined through statistics to be necessary to minimize the likelihood of error in reaching conclusions about safety (phase 1).

The statistician's work is crucial both to the justification of the studies proposed for all phases of IND research and to the related study designs. Scientific determination of the necessary size of the initial patient population (phase 2) must depend largely on a statistical estimate of the smallest number that would be sufficient, because the fewer people exposed to the risk of a new drug product, the better. Both risk and cost are reduced.

Statistics must also project in the IND the magnitude of difference necessary to demonstrate significance in variations between the laboratory values and clinical findings in patients treated with the test agent and those given placebo or standard medication. These determinations, as well as many of the particulars of the selected randomization patterns in the phase 2 and 3 trials, rest on a fundamental ability of statistics, that is to ascertain the likelihood of error in a particular statement and to estimate the confidence that can be placed in any experimental value.

The FDA's decision to allow the investigation of a new drug to enter each of these next phases, and the decision of the sponsor on the value of pursuing the full course of investigations through to the NDA submission, are based largely on the statistician's estimations of the probable outcomes.

IV. PROTOCOL DESIGN

In designing and analyzing the various aspects of a trial, the statistician uses inferential reasoning and methodology. The formation of a testable hypothesis, the creation of a protocol for hypothesis testing, probability estimation, and decision-making all involve inferential reasoning.

The statistician must also be skilled in the description of the results. The choice of statistical method (in conference with the FDA) and the use of graphs, tables, cross-tabulations, and illustrations all use the descriptive powers of the statistician. The persuasive potential of a document relies on the inferential reasoning used throughout its development and the descriptive techniques used in its completion.

The following points should be kept in mind in the design of a clinical research protocol:

1. All members of the team should strive to ensure that the objectives of the proposed study are stated so that the hypotheses to be tested are clearly anticipated, evaluated, and answered by the clinical study.
2. No hypothesis should be put forth for testing in such a complex manner that other hypotheses and assumptions remain bundled up in it unrecognized. Statisticians should collaborate with writers on revisions of the protocol until this has been assured.
3. All substantive assumptions should be articulated. Once made explicit, the clinical and other assumptions necessary to the trial should be examined for their statistical implications. Such assumptions include those inherent in statistical methods and in the computer programs to be used for analysis. Others are clinical assumptions, such as the enrollment and grouping together of patients with two forms of a particular disease based on the idea that, with regard to the therapy being tested, they are the same.
4. Clinical decisions in protocol design are tantamount to statistical decisions. Probing by the statistician during protocol design may prompt clinical experts to clarify their objectives and collect data in such a way that individual aspects of the study can be confirmed more precisely. In the case of two forms of a disease, a more careful enrollment and randomization protocol (that does not group everyone together, but stratifies the sample by form of disease) can produce data that will build a more convincing case. This will prove that the therapy does indeed have comparable effects in the two groups, or perhaps does not.
5. Each clinical trial should be designed to test only one, or at most only a few primary hypotheses, each of which should be clearly distinguished from the others.
6. Every effort should be made to have the protocol produce quantifiable data concerning each of the hypotheses to be tested. The statistician should design or review the nature of this quantification to make sure that the raw data collected in the clinical sites to be submitted will be in a useable form.
7. Where it is necessary to incorporate qualitative observations or aspects of patient histories, conversion to quantification with the use of rating scales, which may rely on groupings of synonymous descriptions, should be attempted.

8. The vexing and time-consuming problem of illegible patient records and inaccurate transcription should be solved before or, worse, at the beginning of the study. The solicitation of suggestions from the statistician and data management personnel before finalization of the data collection procedures can go a long way toward speeding the work of onsite CRAs.

It is entirely possible that the statistician will have to provide changes to the clinical protocol initially proposed to facilitate the application of probability theory to decision-making. Though statistics is the science devised to make decisions possible in the face of incomplete knowledge, all of the experiments should be designed to provide information that is as complete and specific as possible.

The statistician is responsible for determining whether the observed results can be generalized to the patient population that the sponsor company hopes to target. The target population must be carefully considered, and the proof of its need for the proposed therapy must be defined with the utmost care through appropriate enrollment and inclusion/exclusion criteria. Handy, familiar jargon such as "long-term, chronic, mild to moderate hypertension" should be pinned down within a numeric range for systolic and diastolic blood pressure values, duration since onset, and any other quantitative measures possible. This will make data collection and evaluation feasible and more worthwhile.

In addition, the protocol should call for examination of the demographic characteristics of these patients, medical history, physical examination, and other patient characteristics known by the consultant clinicians and cited in the literature as possibly significant. Some of these may simply be recorded and later duly noted with relation to the test product's effects, and others may serve at the outset as part of the inclusion/exclusion criteria. As always, numerical definitions are more useful but may not be appropriate to all demographic criteria.

V. TARGET POPULATION AND STUDY ENDPOINT

A most crucial term to be defined is "risk." The terms of its description should include, first, the patient's response to the study drug in comparison to response to control therapy or other alternative forms of treatment or no treatment at all and, second, the acceptability and duration of drug-free pretreatment periods, placebo controls, potential adverse drug reactions, and duration of exposure.

Obviously, the inclusion/exclusion criteria should result in a patient population that is as large as is scientifically justifiable and desirable (i.e., large enough to detect the desired difference at the stated probability levels.) In the earliest clinical trial (phase 1), the potential risk entailed in administering a new drug to humans for the first time dictates that the trial group be as small as necessary to provide strong evidence of safety. In early efficacy studies, it is usually preferable to test a homogenous subset of patients to better control extraneous variables. In later studies (phase 3), it should always be borne in mind that the labeling claims for the drug will have to be limited to the population in which efficacy has been proven; thus, in phase III trials, more heterogenous populations should be used.

The narrowing of the potential patient population by exclusion criteria and the segmentation of the included population both increase the specificity of the study. The statistician may delight in the increased power of prediction and reduction in experimental error made possible by this specificity, but these objectives must be balanced with pragmatism. How difficult is it to recruit patients of the narrowly defined condition, as opposed to the more broadly defined disease? The statistician, while eyeing the advantages to be gained from specificity, must recognize the valid arguments of the tactician who points out the practical problems of recruitment.

After careful statistical, clinical, and pragmatic evaluation, the study population may be defined.

The following should be kept in mind when a treatment population and the study endpoints are defined:

1. The team members should provide an exposition of the logic governing the identification of the target patient population and the statistical validity of the intended sample study population.
2. This justification should address both of the concerns that are fundamental to all clinical testing of all drugs and devices: safety and efficacy. Documentation for the early-phase studies will emphasize issues pertaining to safety; later studies will emphasize the anticipated efficacy, addressing any safety concerns that may have come up in earlier studies.
3. The criteria for patient inclusion and exclusion from the study should be made clear. The method of randomization or assignment to active medication or placebo should be spelled out.
4. Risk to the patients in all parts of the study should be determined in advance to the degree possible.
5. The documentation should provide justification for the way in which variables are to be modified by patient randomization and other features of the study design.
6. Variables slated for systematic observation according to the protocol should be ranked as either primary to the determination of safety or efficacy or of secondary interest.

7. The timing of interim analyses to determine the importance of observed variables should be justified; issues of bias that may arise when interim analyses are made should be addressed as necessary.
8. The methods by which data are collected and recorded should be set forth.
9. It is important to document that both the quantitative and the qualitative measures to be used are as free from bias as possible. Rating scales to be used by clinicians merit special attention. The objective here, as elsewhere, is to characterize the data in advance as valid, reliable, and accurate within reasonable expectations.
10. Before the study begins, the team should agree on a definition of treatment compliance and on the statistical methods to be applied to the various types of noncompliance that may arise. Having these methods in place at the outset will prevent questions about the validity of the analysis at the end of the trial.
11. For the same reason, the methods of data description, analysis, interpretation, and reporting should be stated and, before initiation of the study, should be presented to FDA for confirmation that they are appropriate and unlikely to foster or conceal bias.

VI. THE STUDY DESIGN

As stated above, one fundamental of good study design is the creation of patient selection criteria that will result in a study population that is truly representative of the entire target population without inadvertent bias in the patient enrollment. This and other fundamentals of good study design are discussed below.

A. Literature Review

Although the statistician should begin to figure estimates of sample size (N) and significant differences in clinical findings by consulting with the clinicians, it is recommended that the crucial N value be determined after a thorough review of the pertinent medical literature. Additionally, the FDA can be an extremely valuable source of unpublished literature. The FOI Act makes it possible to obtain the SBA for any marketed drug. Also, for many drug classes, the FDA has guidelines that will assist in sample size determination and study design.

Previous clinical trials involving similar patients may provide estimates of sample size calculations, means, standard deviations, or, in the case of a binary response variable, response rates for the control group(s), as well as ideas for analysis and display of results.

B. Sample Size and Significant Difference

To be accepted as representative, the sample should be of sufficient size (i.e., adequate to allow for the use of statistical probability in generalizing to the target population). In the early stages of planning, the smallest meaningful difference between treatment groups must be determined. The sample size is estimated on the basis of the projected magnitude of difference to be detected and the magnitude of sample variations; these projections, of course, may be exceeded or not found in the trial. There are numerous tables, formulas, and computer programs for determining the sample size necessary to give adequate statistical power for the agreed-upon significant differences.

However, practical considerations may place limits on the sample size. The population of actual patients estimated or known to belong to the target population may be very small. The financial and time constraints set by management will probably determine the largest possible N. Another limit, existing to varying degrees in all trials, is the factor of attrition. Patients drop out, are noncompliant, or are not available. The enrollment possibilities must therefore exceed the calculated N. The statistician must know of all such limits with as much specificity as possible.

If it turns out that the ideal sample size is actually available, so much the better. However, sample sizes ranging around the one agreed to by the clinicians should be worked out, and the values for varying statistical power (the probability of detecting a given difference if it truly exists) should be calculated. If the sample size calculated to be optimal is unworkable because the largest N feasible in the real world is smaller, then the statistician must have the other team members consider the following four alternatives:

1. Reevaluate the specifications of the clinically meaningful difference between the study groups.
2. Research the possibility of devising methods to reduce variability in the study.
3. Go ahead with the study as is, with the awareness that a potentially inadequate sample size may be enrolled and followed to a satisfactory, evaluable end point. (In certain specialties this may be acceptable, though looked on less favorably as time goes on.)
4. Refrain from doing the study, inasmuch as its findings will be of questionable value at best. This last alternative, though no doubt attended by disappointment, will also prevent the waste of funds and effort.

Be particularly aware that the abandonment of a planned study may be especially wise if the protocol did not include a placebo control. There is an assumption implicit in studies of active agent versus active agent, which is that both are better than placebo. This makes it absolutely necessary to have an adequate sample, thus adequate statistical power, to make any claims of equivalency and efficacy.

If the projected magnitude of difference between the groups is actually substantially exceeded, a study with an "inadequate" sample size may be accepted as convincing. It is also possible that clinically impressive results will be found in the absence of documentation of the projected significant values. If so, the statistician may offer the encouragement that power analyses performed after the fact may suggest that the projected sample size was too small for the purpose specifically intended, and the study results do not support the conclusion that the drug is ineffective. Though such a study may not satisfy the FDA, reanalysis of its data may prove useful.

C. The Role of Placebo

The next fundamental is to devise a study in which the new treatment will be compared with placebo and, if possible, a standard therapy, that is, new drug versus standard drug versus placebo. A placebo-controlled study for which the statistically significant differences have been predetermined allows a thorough assessment of the active therapies used, and the possibility of confirming that at least one of them is superior to placebo.

To be certain of this confirmation, bias should be precluded from the patients' reported responses and the doctors' assessments as much as possible. A careful strategy can often make the different therapies and placebo indistinguishable. The whole point of a placebo relies in its being indistinguishable from the active agent of interest; usually this is easy enough to arrange.

However, it is not always so easy to get two medications, therapies, or procedures to be indistinguishable to patients, much less to all the nurses and doctors involved. For instance, one drug may require intravenous administration, while the other is an oral medication. The two drugs may have very different durations of action or very different side effects, so that both the patients and all the clinicians know which patients are on which medication. The action of the active agent may be quite obvious, and the effect of the placebo (nothing) is nothing, so that even if patients do not deduce what arm of the study they are in, the clinicians will probably catch on, and the problem of bias in the observations surfaces.

Although the use of a placebo control is generally preferred, this study design is not always possible because of ethical considerations. Fatal or potentially fatal illness, such as malignancy, severe depression, or infections must not go untreated in randomly selected patients simply to satisfy the ideal study design. However, if no placebo is used and the new therapy can be compared only with another therapy, the analysis of the results should at least address the assumption that both of the therapies used were assumed (and not proven in the present study) to be superior to placebo.

It is the use of placebo that makes possible an assessment of the sensitivity of the trial, through comparison of the standard therapy with placebo, and comparison of the new treatment with both placebo and the standard treatment. In trials that lack placebo control, comparability of the two active regimens is taken to be proof of the new agent's efficacy. Again, the statistically significant differences in the final data should be predetermined. If numerical differences that are statistically significant are determined in advance, comparability of the new and old drugs can be demonstrated with objectivity, or possibly the superiority of the new agent over the old will be found.

The statistician should note when interpreting the statistical analysis that the failure to find significant differences in the final data might be attributable to the quality of that data as recorded, perhaps to the quality of the study design or to insufficient sample size, therefore insufficient statistical power. Bias in clinical findings, particularly in nonblinded or poorly blinded studies, is one possible cause.

Lacking the placebo control, the statistician is dependent on outside sources of information to assess the significance of the findings. When validation or qualification of findings is required, previous studies with similar patient populations, drug dosages, study design, and implementation are commonly used to check and interpret the results of studies that do not use a placebo.

D. Randomization

No matter how many groups the enrolled patients are assigned to, the assignment method must not introduce bias. With regard to demographic, medical, and other pertinent baseline variables, the groups must be comparable to the extent possible.

Randomization should be done in blocks, to ensure that treatment group enrollment will be balanced as the study proceeds. In multicenter studies, each site should have its own projected number of patients, and the randomization should be done by that site, again to make sure that the treatment groups are the same size. When *k* is a multiple of the number of treatment groups, within each group of *k*, patients should be separately randomized. If there are only two treatment groups, for instance, randomization of blocks of four patients might be either ABAB, AABB, BAAB, or BBAA. Stratification may be necessary if there are identified factors, such as sex, known to have an influence on the results. Again, the objective is to have the same proportion of patients from the different strata in each treatment group. Whether the randomization pattern is simple or complex, comparability is the key.

E. Some Basic Study Designs

The simplest and probably most frequently used design for a clinical trial is the parallel-group design. Eligible patients are randomly assigned to receive one and only one of several treatments or treatment regimens.

Paired-comparison designs, in which each subject serves as his/her own control, are also common.The same subject might receive both treatments at the same time, such as on two distinct and separate lesions on the body. Care must usually be taken in the protocol to make sure the separately treated areas on the same patient are as equivalent as possible in the disease under study.

In crossover design studies, patients receive the treatments one after the other. The order of treatments is assigned to each patient by randomization. The crossover trial is only feasible when it is possible first to rule out effects, whether physical or psychological, that carry over from treatment during the first period of the study (through the washout period) into the next treatment period. Second, it is possible to ascertain that the disease state has returned at the beginning of each treatment period to the baseline at which it stood at the trial's outset. If it is not possible to rule out a change in the pathologic condition, or if carry-over effects are found, the statistician may be forced to analyze only the first period data and to do it as a randomized parallel-group design with an attendant reduction in statistical power.

When investigation has progressed to the point where safety is not the overriding issue, and the objective of the trial is to evaluate a simple efficacy end point, the design of choice is a sequential design. The foundation of such a study is a predetermined plan for making the decision to terminate the trial after specified numbers in each group have been evaluated. This strategy minimizes the number of patients exposed to an inferior treatment, but the relatively early termination and the possible smaller number of patients enrolled will obviously limit the information on adverse events and other safety end points.

VII. SOME BASICS OF STATISTICS

Statistics is the science of drawing inferences under conditions of uncertainty, through application of logical and mathematically sound methods for collecting and evaluating experimental data.Good statistical methods offer the power to get the most information out of a given set of data through efficient design and evaluation. Statistics offers a standard method for judging experimental data. However, it is not a substitute for good experimental technique and does not replace sound professional judgment in the interpretation of the results of an experiment. It is, however, a very powerful tool when the statistical analysis is appropriate to the experimental procedure.

After the basic protocol has been worked out, the statistician should prepare a "statistical statement." However, before summarizing what is expected by the FDA in this statement, a quick review of a few of the basic tools of statistics might be worthwhile.

Obviously, not only are the fundamental features of the study design determined, in part, by statistical models, but the trial design in turn dictates the analytical models to be used. Most plans, particularly those for a multicenter study, should allow blocking or stratification of the data so that differences in individual study centers can be accounted for in the analysis.

It is usually required to perform an "intent-to-treat" analysis that will include data on all patients who were enrolled and began treatment, regardless of whether they followed protocol, finished the study, violated protocol, or dropped out.The purpose here is to ensure the safety of the investigational substance, because substantial bias would be built into the overall analysis with the exclusion of patients who could not tolerate medication and dropped out, or who were not helped by the medication and switched to another treatment. In addition, of course, there might be an analysis of the results from all patients who followed the entire protocol properly.The intent-to-treat analysis should include patients who withdrew from the study; the last clinical measurements taken for these patients should be carried forward as the last observation or final score—the so-called end point analysis.

In addition to actually performing the numeric and algebraic manipulations, the statistician should provide justification for the selection of the methods used, as well as justification for all assumptions made. For instance, the analysis plan should identify all important covariates and justify the assertion that they are indeed covariates. If a set of data is assumed to display normal distribution or to lack this feature, the assumption must be made clear, because the selection of an appropriate statistical model depends on the assumption.

There should also be an explanation and justification of the method by which the clinician's words, such as "lethargy," "severe pain," "stupor," etc., are transformed into numbers that can be manipulated in statistical calculations. The coding of case report forms entering adverse event and concomitant medication information, whether done manually or electronically, is obviously necessary. This is easily done with the use of standard references, such as the COSTART and the WHO dictionaries.

VIII. THE STATISTICAL STATEMENT

The justifications of the methods selected for analysis should not wait until it comes time to write and submit to the FDA the results of a clinical test. Both the protocol design and the methods of analysis should be discussed with the

FDA at an early stage to ensure that they will be accepted as scientifically valid. The statistical analysis section prepared after the basic protocol has been finalized should describe the following:

1. Variables that will serve to monitor safety and those that will document efficacy should be justified as those most likely to provide complete information. The primary efficacy variables should be identified, and those that are secondary should be named as such.
2. Explain the methods and precautions adopted to ensure that the raw data are accurate (observed without bias and transcribed or coded without error or distortion), consistent (within a patient's history, a clinician's practice, and the study as a whole), and reliable.
3. Before the beginning of the study, any interim analyses (those planned as checks while the study is in progress) must be described. This type of check will no doubt entail breaking the blinding code, and each "peek" essentially costs the trial some of the potential power of its data. In addition to the schedule of these planned analyses, the statistician should describe the blinding mechanism, the monitoring procedures in general, the variables to be analyzed, and the statistical analyses to be performed using specified significance levels.
4. The statistical methods to be applied to the complete data set at the end of the trial should be described in detail at the outset. Identify the major end points, the statistical methods to be used with data from intent-to-treat patients who dropped out, all planned comparisons, planned subgroup analyses, the criteria by which response variables will be categorized, and the efficacy criteria against which the endpoint values from the entire data set can be tested.
5. A justification for the sample size should be provided. That is, what is the magnitude of the differences this clinical trial is expected to detect and what is the expected variation of the response variable.

IX. THE DESIGN OF METHODS AND THE FDA

Above all, in seeing the statistical statement through to its full usefulness, be certain before the study begins that any questions raised by the FDA statisticians (or other experts) have been worked out in satisfactory revisions.

The most difficult thing to understand is that the newest, most highly sophisticated statistical procedures recently accepted by the community of statisticians may not be acceptable to the FDA. In addition, bear in mind that to communicate effectively, you must consider the nature of the audience or critic. Many FDA reviewers have backgrounds in clinical medicine, chemistry, or a variety of specialties other than statistics. The most exciting publication or conference presentation in your field may very well be completely unknown in other professional circles. So it is not terribly surprising that an FDA reviewer who is simply trying to ascertain that your methods will give valid conclusions may not be comfortable with a new method that you are most eager to try out. In fact, he or she might even be suspicious of it. Be pragmatic, if not understanding. Be convincing. Offer from the outset to provide statistical analyses using methods that the reviewers have some confidence in. Work with the FDA biometrician to guarantee acceptance of your methods. Established procedures and the conclusions drawn from them are more easily grasped by the reader and more easily defended. As mentioned earlier, it is common for verification of the results achieved with one statistical method to be worked out with another method in the original submission. This is a good idea, and it offers the opportunity to use the newer method (perhaps in an appendix) where it will be seen to produce the same results, perhaps more elegantly, or even more precisely.

Each division of the FDA is familiar with certain statistical methods and may wish to express preferences or expectations that differ somewhat from those found in another division. Passing up the opportunity to discover these expectations is not wise, as this can lead to very time-consuming, costly reanalyses of data. In the worst cases, where a study design is predicated on statistical models that are found unacceptable, additional data could be required. The crucial communications of a drug research statistician begin with an exchange of documents, letters, phone calls, and face-to-face meetings with the FDA, and should continue in the form of end-of-phase (or presubmission) conferences in which sample formats of proposed tables are discussed, straight through to the textual and graphic communications of the final submission. The file built up as revisions supersede earlier work should be supplemented with accurate and complete written records of all discussions with the FDA.

The following synopsis of the FDA's expectations is based heavily on the "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications." The report will include at least the following:

1. An integration of both clinical and statistical interpretation of the data
2. The statistical model(s) underlying the analysis (documented by literature references, if necessary)
3. The specific parameters and statistical methods applied to estimate and test hypotheses about these parameters (including relevant literature references) to their application
4. Summary statistics presented in a manner that allows reviewers to verify the results of the analysis with the stated significance levels associated with any test procedures identified as being one-tail or two-tail
5. Data listings by variable and by patient in place of a review of the case report form

6. The power against specific alternatives for those tests that fail to reject the null hypothesis for the primary analyses
7. Detailed summaries of safety data (clinical signs and symptoms, adverse events, and clinical laboratory values)
8. A discussion of the inferences drawn from the analysis in relation to the objectives of the study and the clinical/medical relevance of the inferences.

X. CLINICAL STUDY EXECUTION

As investigators create files on enrolled (and excluded) patients, CRAs are probably making periodic checks of the completeness and internal consistency of these notations of patients visits, checking also for protocol violations. This is the first step in what should be an ongoing effort to ensure adherence to the protocol and accurate and complete documentation of all selected variables. Visual and computerized reviews by data managers are the next checks. Records are gathered from the various clinicians and checked again; in these interim reviews of the raw data, the most important objectives are as follows:

1. Perform these checks from an early stage, and frequently, to spot problems and prevent the accumulation of problematic data. Computer runs should be completed, as well as close reading of the individual case reports. It will be easier to spot patterns and instances of data omissions, inconsistencies, irregular relationships between measured variables, and the recording of clinical observations or drug administrations in an improper sequence.
2. Violations of protocol must be identified and characterized, and some member of the team should be dispatched to give the needed explanations and corrective actions. Note especially adherence to enrollment criteria, the drug administration regimen, including the duration of washout periods (if any), patient compliance, and the specified clinical and laboratory observations. The periodic computer checks can identify the site(s), if any, that are outliers from the average of other sites.
3. The protocol has built into it certain assumptions that are critical to the statistical analysis intended and agreed upon with FDA. These assumptions must be protected.
4. The CRAs should have spotted any illegible items on patient records and, by interviewing the clinician, restored the information before it was forgotten.
5. If an adverse event and concomitant medication coding can be started, make sure there are no unexpected problems.

6. As patients drop out of the study (a problem to be expected in all trials), the data should be reviewed to determine the rate at which this is occurring. The period from enrollment, the stage of the protocol at which it occurs, and the reason(s) for each termination should also be determined.

The importance of these safeguards cannot be overstated. If the protocol is violated or the quality of the data is poor, there is hardly much point in performing a rigorous analysis.

In the case of protocol violations, a team member must determine whether this resulted from the clinician's misunderstanding or misinterpretation of the protocol, indifference and sloppiness, inability to communicate necessary information to the patient, or, as happens in rare cases, fraudulent practices. It is very likely that when there have been serious violations or a substantial number of dropouts, the study will have to enroll more patients and be extended beyond the originally projected time frame.

XI. INTERIM ANALYSES

Interim analyses that were justified in the protocol to the FDA should be done, although each usually requires that the results are known to very few individuals. Clinical staff involved in the actual study must be blinded to these results. The planned interim analyses are done for administrative, ethical, or analytical purposes. It is important to be clear about which of the three purposes is intended.

Administrative interim analysis should provide feedback on whether the study is being executed as designed and whether the data are being thoroughly and accurately collected. This is a gauge of the conduct of the study, not of the results. Randomization codes need not be broken.

In cases where safety or ethical considerations make it necessary, a safety committee or ombudsman may be designated at the outset to monitor the safety of the patients. This ongoing responsibility, to discover whether one group is being placed at significantly greater risk, is accomplished within guidelines set forth in the protocol.

Interim analysis can also be done at a specified point in the study to see whether the results are clear. If there is already enough information to conclude that one treatment is significantly better than the other or placebo, then there is no longer any reason to continue exposing patients to inferior treatment. In evaluating interim findings from multicenter studies, care should be taken not to draw conclusions from an unstable database that is not truly representative of the ultimate target population, whether it comes from only one clinic or a few out of many. The smaller the database, the greater the influence of a few outliers. Remember also that in the early days of a trial, the data from the first few patients in a center are frequently of lower quality as the investigator and staff become comfortable with the protocol.Obviously, the treatment codes here are broken and the significance level of results in the final analysis could be affected if the study continues.

XII. OVERVIEW OF CLINICAL STUDY DATA ANALYSIS

Data summary, tabulation, and analysis are finally done after a last quality check of the data for completeness and internal consistency in each patient's records, relative comparability of data from all clinical sites, data transcription or entry errors, etc.

That done, the next step is *not* to do inference tests but, instead to inspect the raw data listings organized by variable, groups of variables, individual patients, and frequency distributions. Note observations or sets of data that are outliers by any large measure and track them as far back as necessary (all the way to the original case report forms if indicated). If the anomaly appears there, seek confirmation from the clinicians. The smaller the sample size, the more important this diligence becomes.

By doing this, the statistician becomes familiar with the strongest data trend and will be able to assess the frequency with which data with a certain variable are missing. This includes rate, timing, reasons for dropout, and some of the other easily noted results.

Now, with this groundwork finished, formal analysis can proceed. This does not mean that all caution can be thrown aside. The computer programs were tried out in the interim analyses or on test data sets, but the statistician should remain alert to the possibility of their errors and to the possibility of inconsistent data. Suspicious findings should be tracked back through the computer program and to the source of the original data.

Comparability of treatment groups, as remarked above, is basic to every clinical trial. Thus, a first step in analysis is to confirm comparability for each baseline variable or relevant combination of variables. If it is discovered that comparability is lacking with regard to disease status, risk factors, or demographic characteristics, the statistician should document the potential effect on subsequent analyses.

Comparability of the treatment groups should also be defined with regard to adherence to the protocol. The various problems created by dropouts have yet to be resolved by a method that is universally acceptable. In fact, analytic methods used to evaluate "nonevaluable" patient data are often sources of critical controversy.

Two basic procedures seem called for: compare the dropout rates and time-to-dropout across all treatment groups, and analyze the intent-to-treat group (all randomized patients). Beyond this, consider two analyses (in addition to intent-to-treat) to assess the impact of the dropouts on the final results: an end point analysis (the last clinical and laboratory observations of each patient) and an analysis of all patients actually evaluated at each of the scheduled patient visits.

XIII. FINAL STUDY REPORTS

In the final study report, review the main statistical features of the investigation, justify the statistical methods used to pool data from multiple independent clinical investigators, and give evidence that the possibility of influence by the investigator as a variable has been worked through.

A. The Efficacy Section

The final report submitted to the FDA must discuss both safety and efficacy. In the efficacy section, a precise definition of which specific patients are included in the efficacy analysis is necessary. The "Guidelines" suggest doing an intent-to-treat analysis, including all patients randomized in the study. This is done in addition to the study sample that is defined as clinically relevant.

Demographic and baseline features of individual patients and the comparability of treatment groups for these features are needed. If the patients in the intent-to-treat analysis and the clinically relevant analysis differ in number and identity, the comparability in both sets must be examined. In multicenter studies, comparability should be assessed both within and across centers. Tabular listings of individual patient demographic and baseline data should be provided.

Efficacy analyses and tabulation of individual patient efficacy data should include the following:

1. The results of analyses planned in the statistical statement presented in the clinical protocol for the study should be provided, including an investigation of the time course of the responses. Explanations must be given if any analyses in the protocol are not carried out or are modified.
2. For multicenter studies, statistical models should include terms for center (study) effects, and treatment-by-study interaction (two-way models) should be tested and examined.
3. For multicenter studies, in addition to the results of the two-way models, the results for each individual center should be provided for important variables.

4. If the size of the study permits, comparative efficacy within relevant baseline or demographic value-defined subgroups should be examined. Only relevant significant findings must be presented, and substantial elements of the inference can rely on descriptive statistics. If relevant, dose-response relationships should also be discussed.
5. In bold print, the guidelines state: **"It is critical that for any table or figure there be clear identification of the data set analyzed, clear identification of what is being displayed through use of good headings, identification of units, and labeling of graph axes, and a clear statement in the text concerning any conclusions drawn from the table."**
6. The report should also contain "data tabulations" for all primary and secondary efficacy variables.
7. Any proposed relationship of response to concomitant therapy or concomitant illness should be clearly delineated. This may also require cross-tabular presentation of data.

B. The Safety Section

The safety section requires the following information and statistical input:

1. A description of the length of exposure to the drug should be included. This is best done by categorization of patients according to duration of therapy using reasonable intervals.
2. All adverse events (not present at baseline or worsened from baseline) should be displayed in tables that provide the number and percentage of patients in each group reporting the adverse experience. Tabulations should also be prepared in which the adverse experiences are grouped by body system and severity. Patient identification including age, sex, height, weight, race, and treatment dose for each adverse experience should be provided in listings.
3. The original vocabulary used by the investigator to describe adverse experiences should be used in listings of the individual final study reports. These should indicate which terms in the coding dictionaries were used for the original terms. These dictionaries will contain a preferred word and usually summarize the adverse experiences by body system.
4. The overall incidence of adverse experience rates should be statistically compared across treatment groups. Analyses also should be undertaken to examine the data for relationships to dosage, duration of treatment, total dose, and demographic characteristics, as well as any other potentially relevant characteristics.

5. A complete listing of each patient's adverse events that provides essential information concerning the reported adverse experience.
6. All patients who left each study because of adverse experiences should be listed. All patients who died during a clinical trial should be noted, as well as those reporting serious adverse effects. (This is a job primarily for the medical staff, but the statistician should ascertain that all such patients have been flagged.)

Normally, the regulatory expectation would be that a second, and independent, study would be conducted to attempt to replicate the study's findings. The FDA may allow exceptions to this rule, and this is usually agreed upon before the phase III study begins.

1. *Important Safety Issues*

Adverse experience data should be evaluated from a variety of perspectives. These could include the following: adverse experience data in relation to both daily dose level and cumulative dosage of study medication; trend analyses for changes in clinical laboratory values for each treatment group; and adverse experience data stratified by organ system, severity of reaction, duration of experience, and age of patient. In addition, consideration should be given to assessing the level of correlation existing between study drug blood levels and adverse experiences encountered (if such data are available).

2. *Interim Clinical Data Analysis*

The FDA's statisticians expect that each clinical protocol submitted will include a description of any planned interim analyses of the data, including the anticipated monitoring procedures, the variables to be analyzed, and the statistical methods to be applied. The latter includes the choice of significance level for each interim analysis, the frequency of analysis, and a declaration of the circumstances under which the study would be terminated before the planned number of patients have been entered into the study.

3. *Other Issues*

If a claim is to be made for superiority of a drug preparation over another such product, power calculations must be performed to support this claim of statistical significance. Similarly, any claim of therapeutic equivalence between a study drug and another product must be supported by appropriate power calculations.

Statistical significance represents a readily determinable value obtained within an appropriate mathematical model. The related issue of clinical significance should not be confused with a statistical calculation. Clinical significance refers to that increased margin of therapeutic response provided by the study drug (when compared with placebo or a reference compound) that represents the threshold level of increase deemed sufficiently important that a clinical therapeutic advantage would be recognized by experts in the field under study.

Proper application of this framework to any analytical situation encountered can be expected to produce the appropriate statistical database that supports acceptance of said claim by the FDA reviewers. This approach provides evidence of a full exploration of alternatives investigated, their relevance to the situation at hand, and the statistical significance levels attached to each finding.

XIV. CONCLUSION

The statisticians and the data management and clinical teams must work together during virtually every phase of a clinical research project. Beginning with an assessment of the preclinical laboratory data, to the safety analyses of a phase 1 trial, through the massive amount of efficacy and safety data generated by possibly thousands of patients in a phase 3 trial, the statistician can provide important insight into individual study design and the overall direction of the clinical research project.

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The Management of Clinical Studies

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I. OVERVIEW

Before clinical research studies are done, researchers have very little knowledge about the drug being investigated. Preclinical testing provides some information on toxicity and pharmacological activity, but the drug's potential effect in human subjects is still unknown. Each phase of the clinical research trial uses and builds on information obtained from the prior research stage. Clinical research designates an activity designed to test a hypothesis and to permit conclusions to be drawn, thereby allowing us to develop or contribute to increased knowledge shown in theories, statements of relationships, and principles. Its purpose is to distinguish the effect of the drug being studied from other influences—spontaneous change, placebo effect, or biased observation. The research to be conducted is usually described in a protocol that includes a statement of the study's objectives, subject selection criteria, a description of the study design, and the clinical procedures that enable the protocol objectives to be achieved. In the drug development process, results from the first human studies provide the foundation for further development, may streamline the development process, or may be the final step in terminating the development of a compound. The benefit of a clinical study in healthy subjects is enhanced by the performance of well-designed and well-executed protocols. The initial study should be designed on the basis of the insight into safety and tolerability of the compound obtained from preclinical results.

In clinical research studies involving human subjects, respect for individuals demands that every subject enter into research voluntarily and with adequate information. Learning what will in fact benefit the subjects may require exposure to risk. This obligation affects the investigators and members of their institutions, who are obliged to give forethought to enhancing the benefits and reducing the risks that might occur from the research study.

The investigator has the ultimate responsibility for the successful completion of a clinical trial. By complying with good clinical practice, the investigator provides public assurance that the rights, well being, and confidentiality of study subjects are protected and that study data are credible. The investigator must also adhere to the Code of Federal Regulations (CFR) governing the drug development process found in 21 CFR Parts 50 and 56, which deal with the protection of human subjects, and Part 312, which governs the IND process and the responsibilities of the FDA, the sponsors, and the investigators. These regulations are issued by the FDA to provide protection for human subjects of clinical investigations.

II. INVESTIGATOR SELECTION CONSIDERATION

Food and Drug Administration regulations require that a sponsor select only investigators qualified by training and experience as appropriate experts to investigate the drug (21 CFR 312.53 (a)). A sponsor may transfer responsibility of investigator selection to a contract research organization (CRO) (21 CFR 312.52). A clinical research associate (CRA), also known as a medical research associate (MRA), clinical research monitor (CRM), or monitor, representative of the sponsor/CRO, who is familiar with the investigational drug and protocol, is assigned to coordinate and initiate placement of the study. The CRA ensures adherence to the protocol and FDA requirements and acts as a liaison between the investigator/coordinator and the sponsor. The CRA should have the scientific or clinical knowledge needed to monitor the clinical study adequately.

In the identification of potential investigators for a clinical study, the following tools can be used:

- Literature searches in the therapeutic area being studied (e.g., JAMA)
- Clinical research directories/professional organizations that provide listings of clinical research professionals (e.g., ACRP, DIA, RAPS)
- Medical/scientific meetings (e.g., ICAC, AHA, ACOG)
- Referrals (used many times after a study has already been started and to further increase enrollment when another study site needs to be added)

The FDA maintains a list of investigators who are ineligible to receive investigational drugs or who have agreed to some restriction of investigational drug use. This list is updated regularly and should be reviewed. After potential investigators have been identified, initial contacts are made to assess their interest in the study either by:

- Initial telephone contact with a written follow-up asking for curricula vitae (CVs)
- Initial correspondence with a telephone follow-up
- Mass mailing of a "generic" letter to many potential investigative sites

The initial screening objective is to evaluate the professional qualifications of the investigator in the therapeutic area of the protocol. For example, if a study is being conducted in hypertension, do not select a gynecologist as an investigator, because no male patients would be enrolled at that investigational site. In addition, an assessment should be made of the investigator's experience in clinical research, support staff availability, access to study subject population, any current commitments (competitive studies), and past track records in fulfilling study enrollment.

It is very important to keep in mind that approximately 80% of drugs studied never reach the marketplace. Many of these drugs are discontinued because of toxicity. Therefore, in the selection of investigators to conduct a clinical study, it is very important that they be committed to conducting the study in accordance with the relevant protocol and that they personally supervise the investigation and report all adverse experiences that occur.

III. RUNNING A PROTOCOL

A. Prestudy Site Visit

A prestudy visit is conducted after the initial investigator contact to assess if the investigator and staff are qualified to conduct the clinical study.

The following assessments are reviewed at the prestudy visit:

1. Investigator qualifications: The investigator must clearly understand and accept study obligations. A current medical license must be available.

2. Staff qualifications and availability: The investigators' study coordinators (also called research nurses, clinical research coordinators (CRCs), or study nurses) play a key role at the investigational site. Their availability and experience are assessed because they screen and enroll subjects, complete subjects' case report forms (CRFs), maintain source documents, follow and assess subjects throughout the study, and have more interactions with the CRA and representatives of the pharmaceutical study during study conduction.

The personnel required for specialized responsibilities (e.g., phlebotomist, technician) to support the study should be reviewed.

It is very important to assess the qualifications and availability of the subinvestigators conducting the study with the principal investigator, who is a field expert, as the subinvestigators will be responsible for performing the majority of study procedures and reporting serious adverse events.

3. Adequacy of facility and drug/device storage: The facility, equipment, and location must be adequate for conduction of the study. Adequate storage space with acceptable environmental conditions must be available to store study medications. The storage area should be securely locked and accessed only by the research staff. A locked cabinet within a locked area is generally preferred. Over-the-counter medications used in clinical studies are also securely locked, because these drugs are often stolen.

4. Availability of subject population: Assess the plan for patient recruitment. Ascertain the anticipated rate of enrollment and the accessibility to an adequate number of suitable subjects to conduct the study. Note subjects in waiting area of investigational site/office. The need for advertisement is reviewed.

5. Understanding investigator responsibilities: The investigators must understand their obligations to obtain informed consent in accordance with 21 CFR Part 50 and to obtain IRB review and approval of the clinical investigation before a study is initiated. They must ensure continuing review of the study by the IRB in accordance with 21 CFR Part 56 and must keep the sponsor informed of such IRB approval and subsequent IRB actions concerning the study. The investigator must be committed to conducting the study according to the requirements listed on the FDA Form 1572 and according to GCPs. The investigators must accept responsibility for FDA (21 CFR 312.60) and sponsor regulations.

The Investigator's Drug Brochure (IB), which is a compilation of the clinical and nonclinical data on the study drug that are relevant to the study of the product in subjects, is reviewed to provide information on any significant preclinical pharmacology and toxicology data findings. The protocol is then discussed to determine the investigator's understanding of the investigational status of the study drug and the requirements for its accountability. The protocol study objectives, inclusion/exclusion criteria, visit procedures, drug accountability, and adverse event/serious adverse event reporting are reviewed. Particular attention should be given to the inclusion/exclusion criteria, therefore allowing the investigator to ask questions about potential deviations that they may note prior to study start.

After the prestudy visit is completed, a report is written documenting site observations and any pertinent discussions. Any unusual observations are also noted (e.g., outdated equipment). A follow-up letter is sent to the investigator stating the qualification status for participating in the clinical study. If the investigator is qualified, the letter will request a list of the following documents to be sent to the CRA before a clinical research study is started.

1. Protocol page, signed and dated by the investigator to document investigator and sponsor agreement to the protocol
2. Signed and completed FDA Form 1572 (Statement of Investigator), which contains the following information:
   a. Name and address of investigator

- b. Name and address of any medical school, hospital, or other research facility where the clinical investigation will be conducted
- c. Name and address of clinical laboratory facilities to be used in the study
- d. Name and address of the IRB that is responsible for the review and approval of the study
- e. Names of the subinvestigators (e.g., research fellows, residents, associates) who will be assisting the investigator in the conduct of the investigation
- f. Name and code number, if any, of the protocol in the IND identifying the study to be conducted by the investigator

The back of the form needs to be signed and dated by the investigator and a box checked as to what phase of study is being conducted.

3. Curriculum vitae of the principal investigator and all subinvestigators listed on the FDA Form 1572 in order to document qualifications and eligibility to conduct trial or provide medical supervision of subjects.
4. Financial aspects of the study documented in an agreement between the sponsor and the investigator/institution.
5. Institutional Review Board letter of approval for protocol, informed consent, advertisements (newspapers, flyers, television) to be used to recruit study subjects and any other written information to be provided to subjects.
6. List of IRB members and their qualifications or IRB assurance number.
7. Laboratory license, normal laboratory values, and the laboratory director's CV for each investigational site is collected, unless a central laboratory is being used (the central laboratory will send documents to the CRA, which then will be forwarded to each participating investigational site to insert into its investigator's binder).
8. Letter of agreement/letter of indemnification from the sponsor that should indemnify the investigator and institution against claims arising from the trial, except for claims that arise from malpractice or negligence.

When all regulatory documents have been collected and reviewed, an initiation visit can be scheduled with the investigational site so that study recruitment can start.

B. Investigator Meeting

An investigator meeting may be held before all participating investigators' regulatory documents have been received by the sponsor. If the research protocol is still a "draft" version and has not been finalized by the sponsor, this meeting provides investigator input and feedback into the conduction of the protocol. The final changes and outcome must then be agreed to by all present at the meeting.

The meeting is usually conducted when a protocol is final. This allows all study investigators and coordinators to meet the sponsor staff, ask questions, and see other participating centers. The objectives of the meeting are:

1. Review preclinical/clinical findings on the drug being studied.
2. Discuss the protocol design and objectives.
3. Provide common training among all study centers.
   a. Case report form completion is discussed.
   b. Central laboratory procedures for collection of specimens or specific measurements (e.g., bone density) is reviewed.
4. Review good clinical practices (GCPs)
   a. Investigator's responsibilities
   b. Serious adverse event reporting
   c. Investigational review board
   d. Drug supplies/dispensing

The meetings typically are 1 full day. Name tags are given to all present at the meeting. An agenda outlining the meeting contents and time of discussion is provided. Because of the time constraints of many investigators, the protocol design and efficacy and safety parameters should be discussed in the morning, so that if the investigator must leave the meeting, the most critical information has been discussed.

C. Study Initiation

After an initiation meeting has been verbally scheduled, a letter is sent to the investigator confirming the date and time of visit. All research personnel who will be participating in the study should be present, and enough time should be allowed for thorough review of the protocol and study procedures.

Prior to the meeting, the following items are sent to the investigators site: study medication, case report forms, investigator binder, and any other necessary supplies. The site should be told that the study drug is not to be opened and inventoried until the initiation visit.

The following items are thoroughly reviewed at this visit:

1. Protocol: The study's rationale, design, subject selection criteria, concomitant medications, visit schedules, and observations and measurements to be made to fulfill the study's objectives (labs, assessments, tests) are discussed with the entire staff conducting the study.

2. Adverse event documentation and reporting: The investigator and staff must understand the regulatory requirement for reporting adverse drug

events. One of the sponsor's most important responsibilities during a clinical study is to report adverse drug events to the FDA. Routine adverse events are described as events not medically serious, are already reported in the investigator's brochure, and are reported to the FDA with the annual progress report. Nonroutine adverse events are serious and/or unexpected. All serious adverse events must be reported to the sponsor as soon as they are known. The investigator and staff must be made aware of the information to be submitted in serious adverse event reports, as follows:

a. Patient demographics: subject initials, sex, race, date of birth.

b. Study identification: Protocol, center number, investigator's name, subject number.

c. Duration of drug administration: Includes start date of drug administration, total daily dose, frequency, route, unit dose.

d. Drug code or name/dose administered and indication for use of drug.

e. Description of adverse event, including the date and time of onset, severity, action taken regarding study drug, relationship to study drug, treatment (including hospitalization), and date and time event stopped/ended. In case of death, autopsy findings are requested (if available).

f. Concomitant drug therapy at the time of the event, including dose and administration dates.

g. Current disease state and other relevant medical history.

Reports relative to the subject's subsequent course (if applicable) must be submitted to the sponsor until the event has subsided or, if a permanent condition, until it stabilizes. It is the investigator's responsibility to provide the information promptly, because the sponsor must report any serious and unexpected adverse events in writing to the FDA and all participating investigators within 10 working days. Fatal or immediately life-threatening drug events require a telephone report to the FDA within 5 working days.

3. Drug supplies/medication dispensing: It is the monitor's responsibility to inventory the study medication and to have the investigator sign the inventory log to acknowledge receipt of the drug. The procedure for dispensing the study drug and completing the subjects accountability log is reviewed.

To ensure strict control over distribution of study medications used in clinical research studies, the investigator is required to maintain records pertaining to the test articles received from the sponsor, the date the drug was received, and the disposition of the study drug, for example, its use by the subjects. If the study medication is sent directly to the pharmacy department or other appropriate department in an institution rather than to an investigator, the pharmacy or other department may distribute the drug to the investigator or the subject and maintain records. The investigator is still responsible for ensuring that adequate records are maintained.

The investigator and research personnel responsible for the randomization of the study drug should follow the study's randomization instructions. Emphasize that the code is broken only in accordance with the protocol and that the sponsor should be notified prior to any unblinding.

4. Case report form completion: All study personnel who will be entering data into the CRF should be present for review. The CRF contains all data required by the protocol. Instructions are provided for correct entry of data into the CRF, and the sites are reminded that all areas of the CRF are to be completed accurately. No data fields should be left blank. The abbreviations UNK, N/A, or ND are to be used when information is not known and whiteout or obliteration of data is not permissible. If a correction is needed in the CRF, study personnel are to strike through the incorrect entry with a single line, record the correct entry, and initial and date the correction. In a multicenter trial with many centers, instructions or guidelines for correct data entry on each page can be included in the CRF. This allows for uniform entry of data across many centers.

5. Investigator binder: Request that all study correspondence be maintained in the binder so that all documents can be easily located in one area. The monitor's log is completed at every trip conducted by the monitor, and the patient screening log should be kept up to date. The sponsor is responsible for ensuring that an up-to-date investigator's brochure (IB) is available to document that the investigator is informed promptly of relevant information as it becomes available.

6. Clinical records: Two types of records are kept regarding a clinical investigation: (a) case history records (source documents), and (b) the study protocol and related documentation. The investigator is required to prepare and maintain accurate histories that record all observations and other pertinent study data about each subject enrolled. To substantiate that each subject meets the entrance criteria, records of the subject's medical history before entry into the study are maintained. Source documents include the following: documents that support data in the case report forms, information obtained from tests and examinations (e.g., physical examinations, laboratory results, x-rays), consultations, concomitant therapy, diagnoses made, and development of any intercurrent illnesses. Additionally, correspondence sent to, or received by, the investigator from the sponsor and the monitor, including the protocol, informed consents, records of IRB approvals, and any other communications/actions pertaining to the study must be maintained.

7. Monitoring requirements: Regularly scheduled monitoring visits will be conducted as soon as subjects are enrolled in the study to verify the following: the rights of the subjects are protected; the data being collected are accurate, complete, and verifiable from source documents; the trial is being conducted according to GCPs. These visits will provide time for the investigator and staff to ask questions and talk about the progress of the study. It should be emphasized that, at the monitoring visits, time must be allotted by the study coordina-

tor to review case report data, make corrections, and obtain answers to any questions that arise from reviewing documents. There should be a suitable work area for the monitor, and subjects' case report forms with their source documents must be available for review.

IV. CLINICAL STUDY CONDUCT

A. Investigator's Site

After an IRB has approved a protocol and consent form and the initiation visit has been conducted, subjects may be recruited by the participating investigational centers into the clinical research study. Each subject must sign an informed consent prior to the initiation of any screening procedures that are performed solely for the purpose of determining eligibility for research. The informed consent process permits the investigator or study coordinator and the subject to exchange information freely and to ask questions about the research study being conducted. Each subject must be advised during the informed consent process of the extent to which confidentiality of records identifying the subject will be maintained and the possibility that the FDA may inspect the records. Subjects' names are not usually requested by the FDA unless a particular record requires a more detailed study of the case or there is reason to believe that the records do not represent actual cases being studied. Proper selection of subjects is crucial, because artifactual adverse events due to improper selection of subjects or incorrect drug relationship may kill or at least retard a potentially efficacious drug.

Once the informed consent has been signed by the subject and by the person explaining the study, a copy of the consent must be provided to the subject. Regarding subjects' medical histories, it is very important to define the history well to avoid recording unnecessary adverse events during the study. The following is an example of an adverse event captured incorrectly: a subject has a history of bursitis (not told to the investigator at screening) and takes Advil as needed. After the research study has proceeded for months, the subject arrives at an office visit complaining of shoulder pain, having been taking Advil. This complaint would be recorded as an adverse event, as it was not mentioned previously in the history. If bursitis had been captured at the start of the study, only the Advil would need to be listed on the concomitant medication page in the case report form. Another item frequently missed in the collection of medical history is a history of allergies.

Prior to study entry, the subjects undergo a battery of prestudy parameters as dictated by the protocol. These parameters may include, but are not limited to, medical history, physical examination including vital signs, clinical laboratory tests, and electrocardiogram.

When all the study entry requirements have been satisfied, the subject is enrolled into the study, and the investigator has the responsibility to assure that all data are accurately collected and all adverse events are thoroughly evaluated, treated, and reported. Investigators must ascertain, to the best of their ability, the possible relationship of the drug to a particular adverse event.

B. Monitoring

The most effective way to assure that, throughout the clinical study, the investigator is fulfilling the obligations as set forth in applicable regulations and that the facilities used in the study continue to be adequate, is through periodic visits by the CRA. The CRA should schedule an appointment with the investigational site well in advance of the scheduled date, allowing ample time for the research staff to gather all relevant data, complete case report forms, and acquire any medical records required. The visit time and date should be documented in a letter by the CRA to the investigator. This letter serves as documentation and record of notification and should be filed in the investigator's binder "correspondence" divider, at the site. The study site is visited by the monitor to assure the following:

1. Adherence to protocol and any approved amendments and to specified functions that are being performed by authorized study staff.
2. Informed consents are signed and witnessed before the subject has entered the study.
3. Source documents are accurate and up to date.
4. Case report form data are complete and can be verified with the source documents. Case report forms should be completed with a black ballpoint pen, and the print should be legible. Ensure that corrections, additions, or deletions are made, dated, and initialed by a member of the research staff authorized to initial CRF changes for the investigator. Laboratory parameters that have to be transcribed into the CRF must have each data point reviewed closely. Original reports (e.g., electrocardiogram, X-ray, Pap smears) should have copies made and inserted into the CRF. To maintain confidentiality, these reports need to have the subject's name blacked out, leaving only the initials visible.

It is very important to note any trends in the data and in adverse events being reviewed. If similar reactions are being noted in a number of subjects, this finding should be discussed with the investigator and the medical director at the sponsor facility. Careful review of changes in the same laboratory parameters among subjects can provide a better understanding of the study drug's effects.

The investigator must sign and date the final end-of-study (termination) page of the CRF verifying that the data entered are accurate and complete. This page is completed after the study procedures and visits per protocol requirements have been completed; all applicable laboratory test results have been received and reviewed; and final drug accountability is performed. If, after completion of the final page, a correction/deletion is made into the CRF by the research staff, the investigator must re-sign and date the page.

1. Deviations from the protocol have been communicated to the sponsor before continuation of the subject in the study is allowed.
2. Records of drug disposition, including dates, quantity, and use by subjects are being maintained to assess compliance.
3. Adverse events/concomitant medications are recorded according to protocol. Serious adverse events have been appropriately reported within the period required by the protocol, GCP, the sponsor, and the FDA.
4. All enrolled subjects who withdraw or drop out of the study are reported and documented in the case report form. The investigator should, while fully respecting a subject's rights, make a reasonable effort to ascertain the reason for a subject's withdrawal from the study, although a subject is not obliged to give a reason.
5. Check regulatory documentation on file (investigator binder)/IRB correspondence.

The case report form pages, reviewed and corrected, should be pulled to take back to the sponsor's office. Many CRFs are printed on three-part NCR paper. The two top pages—a white page on top (original) followed by a yellow page (data management)—are the pulled pages, and the bottom pink sheet is left in the CRF as the investigator's copy. Other copies, such as laboratory reports and electrocardiograms, are also brought inhouse by the CRA.

After each monitoring visit, a report is sent to the investigator summarizing what was reviewed, and any findings are noted. A monitoring report is completed by the CRA inhouse to maintain a record of the findings, conclusions, and action taken to correct deficiencies for each onsite visit. This record enables the FDA to determine that a sponsor is fulfilling its obligations in monitoring the progress of a study. The record should include the following elements:

1. Date of visit
2. Name and title of the individual who conducted the visit
3. Name and address of the investigator and who was present during the visit
4. A summary of what was reviewed
5. A statement of significant findings, deviations and deficiencies, conclusions, and any action taken, or to be taken, or action recommended to assure compliance

C. Study Closure Visit

The purpose of this visit is to retrieve all remaining supplies and prepare the site for a potential study audit. An appointment is scheduled with the investigator, and instructions are given to have any outstanding CRFs completed, and all study drug should be accounted for. The investigator must be available at this visit to answer any questions that may arise. All of the following tasks are completed at this visit:

1. All outstanding CRFs are pulled.
2. Study issues are finalized.
3. Regulatory records are checked for accuracy.
4. Study drug and other supplies are accounted for, packaged, and returned to sponsor.

The investigator must notify the IRB that the study has ended. The final number of subjects who completed the study, the number dropped and the reason, and a list of adverse events should be provided for the IRB meeting. A copy of the IRB notification letter, which serves as a record of study closure, must be sent to the CRA inhouse for the investigator files.

Investigators are required to retain records for IND studies for 2 years after the date of marketing application approval of the drug for the indication for which it was being studied. If no application is filed or if the application is not approved for the indication, the records are retained for 2 years after the investigation is discontinued and the FDA has been notified of that fact. Retention of complete records is essential to establish validity and completeness of a report on a clinical investigation submitted to the FDA in support of an application for a research or marketing permit.

The investigator may retain records either in their original form or by microfilm, microfiche, or other accurate reproductions of the original records. If copies are used, they must be legible, and the investigator must assure that such reproductions are true and accurate copies of the original. The FDA may audit any records that might support microfilm or other stored data. These records must be maintained just as paper case report forms.

If an investigator relocates, records can be transferred to the custody of another person who will accept the responsibility for them. Notice of transfer is to be given to the sponsor in writing.

V. INVESTIGATOR DISQUALIFICATIONS

The investigator must conduct the clinical research study in accordance with the protocol agreed on by the sponsor. The investigator should not implement any deviation from, or changes in, the protocol without agreement by the sponsor and prior review and documented approval from the IRB. An investigator who has repeatedly or deliberately failed to comply with FDA requirements and has submitted false information in any required report may be disqualified (21 CFR 312.70).

VI. INHOUSE DATA FLOW

After the case report forms are retrieved from the investigational centers, they are typically reviewed by inhouse auditors. Medical review by a physician for safety and efficacy and review of adverse events may be conducted. The data are then entered into a computer database.

Corrections or clarification will probably result from internal review; therefore, an organized system for amending CRF pages must be implemented. Systems for processing CRF pages and completing corrections/clarifications to the CRFs vary from sponsor to sponsor. Two of the most common methods are:

1. Corrections/clarifications may be completed directly on the CRF pages (white and yellow NCR pages are returned to the CRA for correction on-site).
2. Data query forms (or data correction forms) designed to answer queries may be used and require the investigator's signature on the form. The original answered copy is returned inhouse and a copy is left at the investigational center.

Once all queries have been satisfied and the data have been entered, the database is locked. The final clinical/statistical study report can be written.

VII. CONCLUSIONS

The relationship between the research clinical monitor and the clinical investigator (including study coordinator) is very complex. Direct communication between the investigational site and the monitor must occur on occasion to facilitate resolution of questions about study inclusion/exclusion, adverse events, protocol deviations, and procedures. The investigator also provides the link between the IRB and the sponsor. Sponsors rely on the investigator, who assures the sponsor on FDA Form 1572 that the study will be conducted according to 21 CFR Part 312 and agrees to keep records available for review. Ultimately, it is the responsibility of the investigator to conduct the study according to GCPs, and the monitor must assure that the protocol is being followed and subject safety is being maintained.

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Obligations of the Investigator, Sponsor, and Monitor

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I. INTRODUCTION

The Good Clinical Practices (GCPs) regulations section (21 CFR 312) in the Code of Federal Regulations outlines the responsibilities of the clinical investigator, the drug sponsor, and the clinical study monitor involved in investigational new product development. In addition to this regulated conduct of clinical investigations, each participant has a moral and ethical responsibility for the safety of subjects who participate in these studies. Good clinical practices have long been the norm for the investigator, as written in the 1572 Form; however, the first proposed regulations pertaining to investigator, sponsor, and monitor were circulated in 1977 and 1978. In 1987, 10 years later, GCPs were published as final regulations in the Code of Federal Regulations. Today, investigators, sponsors, and monitors are obligated by law to follow these GCPs.

To conduct clinical research that meets the requirements of the FDA for new product approval, it is essential to understand these regulations and their subsequent impact on the clinical development process of drugs, devices, and biologics.

The 1987 IND regulations specified within the current Code of Federal Regulations identify (more clearly than in previously proposed GCP guidelines) the delegation of responsibilities in the conduct of clinical trials. Not only do investigators have a key responsibility in assessing patients' efficacy and safety response to new drugs, devices, or biologics, but the sponsor and monitor also have equal responsibility for the patients' safety and welfare.

To clarify the people who are obligated under GCP regulations, the following definitions will be applied throughout this chapter:

1. Investigator: The individual who conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to the subject). If an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. The subinvestigator is any other individual member of that team. These individuals are usually licensed physicians or individuals working under the direction of a licensed physician.
2. Sponsor/investigator: An individual who both initiates and conducts an investigation under whose immediate direction the investigational drug is administered or dispensed. This category refers mostly to physician investigators who are conducting clinical research under an investigator IND (see Chapter 3).
3. Sponsor: An individual or organization that takes responsibility for and initiates a clinical investigation. This may be an individual, pharmaceutical company, governmental agency, academic institution, or a private or other organization.
4. Monitor: The person selected by the sponsor who is qualified by training experience to facilitate and oversee the progress of the investigation.

II. INVESTIGATOR OBLIGATIONS

In 21 CFR 312.53, the regulations deal with the descriptive information provided on form FDA 1572, the Statement of Investigator form. Also included in 21 CFR 312.53 are the selection requirements for clinical investigators. Previously, to conduct studies designated as phase 1 and 2, investigators were required to complete a Statement of Investigator form FDA 1572; investigators conducting studies designated as phase 3 or phase 4 completed a different Statement of Investigator form, which was known as form FDA 1573. As a result of the IND rewrite regulations, form FDA 1573 is no longer used for any clinical studies. At present, for phases 1 through 4, only the Statement of Investigator form FDA 1572 is required. This describes the obligations of investigators conducting clinical research. The new information required on form FDA 1572 includes the name and address of any clinical laboratory facility and address of the Institutional Review Board that is responsible for the review and approval of the individual investigators participating in the study. This part also states that the sponsor is charged with the responsibility of selecting qualified investigators who are defined as those capable of conducting the study by virtue of their training and experience. By using the phrase "training and experience," FDA means that clinical investigators conducting a study of a particular disease should have enough experience in the clinical specialty to observe correctly the signs, symptoms, and progress of that disease while experimenting with a new investigational drug. For example, if a new drug is designed for an OB-GYN practice, a pediatrician would not be expected to have the expertise to assess this drug, nor would a cardiologist have expertise in evaluating a gastrointestinal drug.

Investigators are defined as those who have signed and completed form FDA 1572, or sub- or coinvestigators listed on that form, and who are considered to have the academic and experiential qualifications for participating in the clinical program.

The "fine print" on the reverse side of form FDA 1572 is a written agreement whereby the investigator assures the sponsor that he will conduct the study in accordance with the appropriate study plan (i.e., the protocol) and will observe the GCP tenets. Implicit in this agreement is the fact that the investigator will have obtained signed Informed Consent (IC) forms from patients or subjects participating in the clinical research under their jurisdiction. Form 1572 also charges the investigator with the reporting of adverse experiences that occur during the investigation and provides assurance that the investigator has read and understood the investigator's brochure. In addition, he or she assures that all individuals participating in the supervision of any clinical study, under the direction of the investigator, are aware of their responsibilities. Once form 1572 has been signed by the investigator, he or she further assures compliance with the requirements of providing study materials, protocols, and other pertinent information to an authorized Institutional Review Board (IRB) for review. Along with these documents, a CV should be provided along with assurance that the investigational plan set forth in the study protocol will be followed.

To summarize, the primary responsibilities of investigators in clinical trials are the ethical and moral obligations to all the participating patients and subjects in the study. Investigators must provide a measure of safety for each participant in the study so that the patient is protected ethically and morally from any endangerment that might occur during a trial of an investigational drug. After the investigator's responsibilities are outlined and he or she has signed form FDA 1572, any additional information from the sponsor that might be necessary should be requested and any concerns regarding procedures should be raised. An investigator is responsible for: (a) ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; and (b) for protecting the rights, safety, and welfare of subjects participating in a clinical investigation on any unapproved product. Also, the investigators must maintain complete control of drugs under investigation. An investigator shall obtain the informed consent of each human subject to whom the drug is administered and shall administer the drug only to subjects under the investigator's supervision or under the supervision of a subinvestigator responsible to the investigator. The investigator shall not supply the investigational drug to any person not participating in the clinical program.

The investigators are required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall account for and return the unused supplies of the drug to the sponsor, or otherwise provide written documentation for disposition of the unused supplies of the drug. An investigator is required to maintain accurate case histories designed to record all observations and other pertinent data on each individual treated with the investigational drug. (Usually this is accomplished by completing case report forms and maintaining medical records.)

All investigators shall retain records of all subjects enlisted in investigational trials for 2 years after a marketing application for the drug is approved for the indication being investigated. If no application is to be filed, or if the application is not approved for such indication, records must be maintained for 2 years after the investigation is discontinued and the FDA has notified the sponsor of the status of the application.

The investigator shall furnish all reports to the sponsor of the drug. The sponsor is responsible for collecting and evaluating the results obtained. The sponsor also is required to submit annual reports to FDA on the progress of the clinical investigations. Investigators shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the investigational drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately (see ADR reporting Chapter 9).

An investigator shall provide the sponsor with an adequate report shortly after completion of the investigator's participation in the study.

III. OTHER INVESTIGATOR RESPONSIBILITIES

The investigator must assure that an IRB complies with the regulations established in CFR (see Chapter 10) and that the IRB is responsible for the initial and continuing review and approval of the proposed clinical study. The investigator must also assure that he or she will promptly report all changes in the research activity and all unanticipated problems involving risk to human subjects (ADRs) or others to the IRB. In addition, the investigator will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

An investigator shall, upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, copy, and verify any records or reports made by the investigator. The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.

IV. SPONSOR OBLIGATIONS

The sponsor's primary responsibility is clearly delineated in 21 CFR 312.50 and ensures that clinical studies are conducted in compliance with FDA regulations. The sponsor is responsible for selecting qualified investigators and for providing them with the information they need to conduct an investigation in accordance with the published regulations. Usually the sponsor accomplishes this task by supplying the potential investigator with an investigator's brochure and a protocol of the clinical investigation on the agent to be investigated (see Chapter 8). An investigator's brochure contains all information from nonclinical studies and reports, and any previous human efficacy and safety study reports that reflect previous experiences of patients on the investigational agent.

Of primary interest in the obligations is the option of a sponsor to transfer total or partial responsibility for the conduct of a clinical study to a CRO. During the last decade, CROs have played a significant role in new drug development (see Chapter 21). However, CROs who contract with sponsor companies are obligated under the same GCP regulations as defined in this chapter. A CRO may be the sponsor or the monitor with equal obligations as defined in 21 CFR 312. The current regulations noted in 21 CFR 312.52 are specific and require that any transfer, whether in total or in part, be described in writing and agreed to by both parties. The FDA states that any obligations not specifically described by the sponsor in the written transfer of responsibilities will be considered as not transferred to the CRO; the liability for these undefined responsibilities therefore remains with the sponsor. The FDA further requires the CRO (once any transfer of responsibilities has been made by the sponsor) to comply with all applicable regulations, and notes that the CRO is subject to the same regulatory actions as a sponsor if the CRO does not satisfy FDA regulations in the fulfillment of its contracted duties. As a result of these regulations, it is possible for a CRO to act on behalf of a sponsor once this legal transfer of obligations has been completed. Although the CRO must assure complete compliance with the responsibilities assigned (and described in writing), it remains the sponsor's responsibility to ensure the quality and integrity of data generated under the supervision of a CRO. In this situation, the sponsor would be expected to act as a quality assurance auditor of the data, even though assignment for the conduct of a study has been delegated to the CRO. The regulations also charge the sponsor with responsibility for the inventory and control of the drug. Only investigators participating in a clinical trial may receive and have access to investigational drug and materials.

V. SPONSOR AND MONITOR OBLIGATIONS

One of the most important responsibilities of the sponsor is to monitor the progress of every clinical investigation conducted under its direction (21 CFR 312.56). A monitor's obligations, under the auspices of the sponsor, are to ensure that the deficiencies created during the conduct of clinical investigations are corrected or justified by the investigator and that the investigator adheres to the investigational plan (the protocol; see Chapter 8). The appointed monitors for any clinical investigation conducted under a sponsor's IND have an obligation to assure that an investigator is complying with the signed Form FDA 1572 and the general investigational plan, and that the clinical protocol is being followed. If an investigator does not correct his errors and mistakes and no improvement is noted in the progress of the study, the monitor shall promptly secure compliance or discontinue shipment of the investigational drug to the investigator and end the investigator's participation in the clinical program. Another responsibility while monitoring the progress of a clinical investigation is evaluating the evidence relating to the drug's safety and effectiveness. At the same time, sponsors shall make such reports to FDA regarding information relevant to the safety of the drug, as they are required to do under section 312.32 of the FDA regulations.

When a monitor reports an adverse effect to a sponsor during an investigational study, it is the sponsor's obligation to determine whether there is an unreasonable and significant risk to the subject or patient. At that time, the sponsor must determine if the investigational study is to be discontinued. Important among the procedures of reporting adverse effects is the sponsor's obligation to the FDA, the IRB, and to all investigators who, at any time, participate in clinical studies and who are prescribing the experimental drug. Subsequent to this, the sponsor should furnish FDA with a full report of the sponsor's actions and shall discontinue the investigation as soon as possible, and in no event later than 7 days after making the determination that the investigation should be discontinued (see ADR Reporting Chapter 9).

It is important to understand that the obligations of monitors include the responsibility for assuring that all records and data recorded on case report forms reflect valid data gathered by the investigator, and that they coincide with corresponding medical and hospital records of the candidate participating in the investigational study. Detailed auditing and documentation assure the sponsor that the monitor is overseeing the clinical data collected by the investigator and that GCPs are being followed. One misconception of many monitors who audit clinical investigations is that their only task is to assure correct entry of data. In fact, one of the monitor's primary obligations is to note any adverse effects or deviations in laboratory values that could signify a safety problem in investigational study subjects. This is especially true in large multiclinic studies, when many centers are conducting investigational studies following the same protocol, and many monitors are auditing data. If any abnormal reactions or laboratory deviations are noted from center to center, the monitors should compare observations and assess an accumulative percentage of occurrence of these deviations. At times, a sporadic, apparently minor deviation can turn out to be significant when calculated across all centers. If monitors are astute, they can often prevent recurrence of adverse events that might jeopardize the safety of the subjects participating in investigational drug studies.

Another responsibility of the monitor is to assure maintenance of accurate records showing the receipt, shipment, or other disposition of the investigational drug. These records are required to include, as appropriate, the name of the investigator to whom the drug is shipped, the date, the quantity, and the batch number of each shipment. A sponsor shall retain these records and reports for 2 years after a marketing application is approved for the drug, or, if an application is not approved, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been notified. The sponsor shall also assure the return of all unused supplies of the investigational drug from each investigator whose participation in the investigation is discontinued or terminated. The sponsor may authorize alternative disposition of unused supplies of the investigational drug, provided this alternative disposition does not expose humans to risks. Although the overall responsibilities are assigned to sponsors, it is the monitors' underlying responsibility for drug accountability.

In turn, the investigators, during experimental research, are also responsible for record retention similar to that of the sponsor. They are required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by the subjects or patients. The investigator is also obligated if he is terminated, suspended or discontinued, or if he has completed a study, to return all unused supplies of the drug to the sponsor or otherwise provide documentation of how the unused supplies of the drug were disposed. (My recommendation is to always return the unused study medication to the sponsor.) An investigator is required to prepare and maintain accurate case histories (designed to record all observations and other data pertinent to the investigation) on each individual treated with the investigational drug. An investigator shall retain records from the study for a period of 2 years after a marketing application is approved for the drug for the indication for which it was being investigated; again, if no application is to be filed or if the application is not approved for the indication, an investigator must retain records for 2 years after an investigation is discontinued and FDA has been notified. The monitor should assure that all the previous procedures are adhered to and reported in a timely fashion.

An often neglected investigator responsibility is their requirement to submit periodic reports to the sponsor. An investigator should be prepared to provide the sponsor with progress reports. These should include an update of the ongoing investigational trial. Annual reports to the FDA on the progress of the clinical investigations are required to be submitted by the sponsor. These reports contain information based on the investigators' progress reports. Safety reports are another issue. An investigator should promptly report to the sponsor any adverse events that may reasonably be regarded as caused by or likely caused by the investigational drug. Alarming adverse events (i.e., severe adverse reactions that jeopardize a patient's safety in any way) must be reported immediately by the investigator to the sponsor. Lastly, when an investigator has completed or terminated an investigational study, a final report shall be provided to the sponsor. This comprehensive report should be submitted to the sponsor shortly after completion of an investigator's participation in the investigation. The report summarizes the final observations of the study and any adverse events that occurred during the course of the clinical investigation. Monitors should also be responsible for encouraging investigators to complete and submit these reports. In this case, constant follow-up may be necessary. In most cases, the clinical monitor will provide the investigator with these reports. They are usually based on the summary of the closeout visit (see Chapter 12).

Legal repercussions can occur from any neglect of the obligations by investigators, sponsors, or monitors. The Code of Federal Regulations stipulates in 21 CFR 312.58 that FDA can inspect the sponsor's records or reports upon request from any properly authorized officer or employee of the FDA. These inspections normally occur at reasonable times and permit FDA to have access to copy and verify any records or reports relating to a clinical investigation conducted under an IND. Upon written request by FDA, the sponsor may be asked to submit the records, reports, or copies of them to the FDA. Under these regulations, the sponsor is also obligated to discontinue shipments of the drug to any investigator who has failed to maintain or make available records or reports of the investigation. Subsequently, an investigator shall, upon request from any properly authorized officer or employee of the FDA, at reasonable times, permit such an officer or employee to have access to or copy and verify any records or reports made by the investigator. The investigator is not required to divulge subject or patient names unless the records of particular individuals require a more detailed study of the cases.

What are the results if an investigator has repeatedly or deliberately either failed to comply with these GCP requirements, or has submitted false information in any report to the sponsor? First, the Center for Drug Evaluation & Research (CDER) or the Center for Biologics Evaluation and Research (CBER) will furnish the investigator with written notice of the matter complained of and offer the investigator an opportunity to explain the matter in writing. On the other hand, at the option of the investigator, an informal conference could be requested. If the explanation offered by the investigator is not accepted by CDER or CBER, the investigator will be given an opportunity for a regulatory hearing. At this hearing, the issue of whether the investigator is entitled to receive investigational drugs will be addressed. After evaluating all available information, including any explanation presented by the investigator, the FDA commissioner determines whether the investigator has repeatedly or deliberately failed to comply with GCP requirements or has deliberately or repeatedly submitted false information to the sponsor in any required report. The commissioner will then notify the investigator and the sponsor of any investigation in which the investigator has been named as a participant not entitled to receive investigational drugs. If there is reasonable cause for this action, the investigator becomes subject to further investigation for each IND and each approved application submitted to the FDA containing data reported by this investigator. Therefore, every investigational study conducted by this investigator will be examined to determine whether the investigator has submitted unreliable data. Other investigations that are conducted under the same protocol will be temporarily put on hold.

Conversely the commissioner may determine, after eliminating the unreliable data by the investigator, that the remaining data justify continuing other of the same investigations at other sites. However, if a danger to the public health exists, the commissioner will terminate the IND immediately; the sponsor will be notified and will have an opportunity for a regulatory hearing before the FDA on the question of whether the IND should be reinstated. If the commissioner determines that the data submitted are unreliable and data submitted by the investigator cannot be justified, the commissioner will proceed to withdraw approval of the drug product in accordance with the provisions of the FD&C Act. As a result, an investigator who has been deemed to be ineligible to receive investigational drugs will be blacklisted and unable to participate in any experimental studies. The investigator may be reinstated when the commissioner determines that he or she has presented adequate assurances that the investigator will use investigational drugs in compliance with FDA regulations.

In conclusion, before an investigator accepts the responsibilities to conduct a clinical investigation with an IND drug, he or she must be aware of the legal obligations agreed to when form FDA 1572 is signed. Investigators must comply with the protocol and the rules, regulations, and guidelines of GCPs. The investigators must realize that they are subject to a federal offense and can jeopardize their reputation and ultimately their ability to conduct further clinical research. Investigators must know that precise collection of data is mandatory in the conduct of clinical research. Research must be designed to assess the efficacy of the product and, above all, to assure that the safety of the patient remains the primary concern.

The investigators', sponsors', and monitors' obligations must be fulfilled by complying with GCP rules and regulations. Sponsors' and monitors' consistent and persistent managing roles are vital in assuring that each person involved in conducting clinical studies meet their legal obligations. The success of any clinical program will depend on the cooperation, understanding, and compliance of this triad working together. With this agreement of responsibilities and a well organized clinical plan the results can only conclude valid data in support of a new drug application.

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Preparing for FDA Inspections: Manufacturing Sites

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I. INTRODUCTION

A. Purpose of a PAI

The FDA PAI program was intended to have two purposes:

1. To provide an opportunity to perform a full GMP inspection of the applicant's facilities to determine the applicant's capability to manufacture the new drug in the submitted application
2. To provide an opportunity to review the applicant's GMP compliance profile

B. When Does a PAI Occur?

Under the current policy, FDA may inspect an applicant's facilities under any of the following scenarios:

1. Drug products that are difficult to manufacture and replicate
2. Drug products with a narrow therapeutic range, such as drugs used to treat epilepsy, asthma, high blood pressure, and heart disease
3. Drugs that are new chemical entities
4. Drugs that represent a new dosage form for the applicant
5. Drugs to be manufactured by a firm with a history of noncompliance with cGMPs
6. Drugs to be manufactured by an applicant who has not previously submitted an NDA or ANDA

7. Drugs to be manufactured by an applicant who has been manufacturing over-the-counter products and who is seeking approval of its first prescription drug product
8. Other reasons as determined by the local district office

In addition to the above, a firm may receive a PAI for the filing of a supplement for NDA/ANDA changes:

1. Changes in the manufacturer or manufacturing site(s)
2. Changes in the supplier of the active ingredient
3. The introduction of a new dosage form
4. The use of new facilities or equipment or significant changes in manufacturing facilities or equipment

For the suppliers listed in the application, a PAI is valid for 2 years for a domestic supplier and 3 to 4 years for a foreign supplier.

Regarding the manufacturing of clinical supplies, one should not be as concerned with meeting minimum cGMP requirements, but rather documentation and controls beyond cGMPs that would be required to satisfy a future PAI. The PAI actually serves as a second review of the CMC section of an application. The FDA's time frame is to conduct the PAI within 45 days after FDA headquarter's acceptance of the application for filing. If a firm is not ready for inspection (the FDA expects the firm to be ready for a PAI upon submission of the application), it is advised that they notify the local district office and provide a date when they will be ready.

Center for Drug Evaluation and Research had 2,213 requests for PAIs in FY 97, of which 1,426 NDA/ANDA applications were covered under these requests; 1,153 inspections were actually performed covering 866 applications. The number of recommendations to withhold approval of the application out of the 1,153 inspections performed was 186.

II. FOCUS OF THE PAI

The PAI inspection team must determine if there is valid and scientific justification for the failure to report data that demonstrate that the product failed to meet its predetermined specifications. Inspections should compare the results of analyses submitted with results of analyses of other batches that may have been produced. The PAI will determine if data submitted in the application are authentic and accurate and if procedures listed in the application were actually used to produce the data contained in the application. These procedures must be specific and well documented. The PAI, in addition, focuses on the following:

1. An evaluation of the firm's compliance with cGMP requirements, including coverage of the specific batches used to demonstrate bioequivalence
2. An evaluation as to whether the firm has adequate facilities, equipment, procedures, and controls to manufacture the product in conformance with the NDA application
3. Collection samples of the biobatch from the bioequivalence laboratory

Extensive emphasis is also placed on the development of research batches to clinical and production batches and the validation of the transfer and scale-up.

III. GENERAL INSPECTION COVERAGE

A. Points of General Inspection Coverage

1. In-depth evaluation of data to support manufacturing process and controls
2. Data review for clinical and biobatches
3. Comparison between submitted and actual procedures
4. Production controls
   a. Supported with scientific evidence
   b. Qualified and verified to include installation and operational qualification of equipment
5. Technology transfer difficulties
6. Batch production in full-scale equipment
7. Facilities and controls review of bio/clinical batch manufacturing
   a. Qualified facilities; validation of equipment
   b. Accurate documentation
   c. Compliance with cGMPs
   d. Validated processes
   e. Training of staff
8. Review NDA filing
   a. Compare against manufacturing procedures for bio/clinical batches
   b. Check R&D notebooks for development support
   c. Check inventory and receiving records for drug substance (accountability, evidence of falsification)
9. Review validation report to support filed data (to include scale-up equivalency from biobatch to proposed production batch)
10. Review chemical and bioequivalency changes (justification of)
11. Review process, change system, and logs (compliance with SOPs and documentation)

IV. REASONS FOR RECOMMENDATION TO WITHHOLD APPROVAL RESULTING FROM A PAI

The FDA cites the following as the most frequently occurring reasons for disapproval of an application after a PAI:

1. The sponsor's lack of facilities or equipment to manufacture the product
2. Raw material specifications that are not documented in the development report
3. Biobatch and scale-up production lots that differ in formulation and manufacturing procedure
4. A biobatch that is too small or misrepresented
5. Discrepancies in bioavailability studies
6. A scale-up that is not documented or supported with adequate data
7. Manufacturing procedures that are not specific as to manufacturing equipment and instructions
8. Lack of data supporting the processes and controls of the manufacturing process
9. Inadequate development data
10. Insufficient record keeping and controls
11. Discrepancies suggesting fraud or deception
12. The lack of sound validation protocols
13. The lack of validated analytical methods, or the failure of test methods to perform reliably
14. Failure to follow stability protocol or to include stability failures with the filing

V. PAI AUDIT STRATEGY AND GOAL

The goal of a PAI audit is to confirm that the process and controls proposed for the production of the commercial batch will produce a product that is bioequivalent to the clinical batch. The strategy of a PAI audit is to confirm cGMP compliance for all batches produced and to confirm that the biobatch provides an adequate bioequivalence linkage between the clinical batch and the proposed commercial product.

VI. "HOW TO" OF A MOCK PAI AUDIT

The best way to prepare for an FDA PAI is to perform a mock PAI. The mock inspection is usually best performed by an independent auditor who has reviewed the appropriate sections of the submission and has gained some familiarity with the product and the production process used in manufacturing the drug product. The main difference between a routine GMP audit and a PAI audit is that a GMP audit usually follows product flow (materials receipt through distribution of finished product), whereas a PAI focuses on the review of the manufacturing process and controls, and begins with a review of records and the actual submission to the FDA. It is recommended that a flow chart be generated during the cursory review of the production process identifying the processing sequence, components, equipment, parameters, and specifications at each stage.

After a cursory review, the NDA/ANDA submission should be fully received, checking for contradicting information in the various sections of the submission. The FDA correspondence file should be reviewed and assessed as to whether all FDA questions have been adequately addressed. The summary section should be examined for inclusion of all batches used in developmental scale-up and stability studies.

A. Clinical Batch Record

The clinical batch record should be reviewed for GMP compliance and documentation requirements. The biobatch and stability batch records should be reviewed for equivalence to the information included in the NDA/ANDA submission. Process controls, specifications, bioequivalence data, and other information supported with foreign data should be submitted with a certified translation of that data.

B. Batch Size and Scale-up

Regarding batch size and scale-up, a minimum batch size of 10% of the proposed commercial production batch should be used for producing test batches of solid, oral dosage nonantibiotic products. All scale-up procedures should be validated. It is important to keep in mind that the scale-up process should not result in a change in the method of manufacture.

C. Drug Formulation and Development

Regarding drug formulation and development, the safety and efficacy studies should be evaluated to check if they were performed using the formulation for the proposed dosage form. Bioequivalency should be demonstrated if a different dosage form or formulation was used to conduct the study. Proposed changes should be critically evaluated for their impact on product quality, integrity, purity, safety, efficacy, bioactivity, uniformity, and stability. One should ensure that an adequate change control system is in place that complies with the systems and procedures established.

D. Product Components

Concerning product components, the name and address of each source of component used in the manufacturing and packaging of the drug product, as well as receiving and inventory (including reconciliation) records for the active ingredient, should be available. The name, address, and operation of each facility involved in the various steps to produce and test the final drug product also should be available. Approved specifications, test procedures, and results for components used should be given. Lots of components should not be accepted on the basis of the supplier's Certificate of Analysis results unless appropriate validation of the reliability of the test results is available.

E. Physical Specifications

Development of physical specifications for the active drug substance (particle size, density) should be specified. Absence of physical specifications must be justified with supporting documentation and should be part of the developmental report 21 CFR 211.84(d). Impurities should be detected, identified, quantified, and characterized. The USP has a limit of 2.0% for ordinary impurities. Data may be required to support the classification of an impurity as ordinary. The FDA expects complete identification of impurities at levels down to 0.1%. A review of active component specifications should be evaluated for changes during development. Changes or discrepancies should be explained. The impurities profile for the NDA drug substance should not differ from lots used in the toxicology and clinical studies. Specifications and microbiological test procedures should be established for pharmaceutical water. Validation of the water system may be required.

F. Bulk Drug Substances

Regarding production of bulk drug substances, specifications for contaminants should be established for all solvents used in the process. A comparison should be performed between the manufacturer's Certificate of Analysis and the submitted specifications, and any discrepancies should be justified. A full description for the route of synthesis should be given, as this is important for the testing and control of impurities and process solvent residues. The FDA expects that, at the time of submission, it will be determined if the drug substance exists in a multiple solid state form (racemic mixture; stereoisomer) and whether this affects the dissolution and bioavailability of the drug product.

A check on the data should be performed to ensure that dosage forms produced from different manufacturers are equivalent. To demonstrate equivalence, at least one batch of the drug product should be manufactured for each source of the new drug substance to verify for bioequivalence against each clinical batch used in the pivotal studies.

In vivo bioequivalence studies may be necessary for each additional source of new drug substance if the drug product is known to produce bioequivalency problems resulting from the new drug substance.

The FDA requests that, for NDA/ANDA products, one batch of each strength be manufactured from each listed source of active ingredient. Three months of accelerated stability data, including comparative dissolution, should be available for inspection.

Regarding the components of bulk fermentation processes, the strain of the organism used to manufacture the drug substance for the clinical study should be compared with the strain to be used in commercial production. Strain identification includes microbiological, cultural, and biochemical characteristics. A comparison of the media composition and method of sterilization, sterilization parameters, and the pH of the medium after sterilization should be done. All fermentation stages, parameters, and conditions should be described in detail (i.e., temperature, pH) and documented.

With regard to bulk drug substances derived from animals, the following should be specified in the submission:

1. Species and organ or tissue used
2. Conditions for storage and transport
3. Processing conditions (i.e., drying)
4. Impurities

G. Equipment

Concerning equipment, comparability is needed when different pieces of equipment are to be used for production batches. Validation of equivalency may be required.

Mixing equipment should be evaluated for the presence of dead spots, which may affect blend uniformity (i.e., valves and discharge ports). All production equipment should be assessed for suitability of use in the manufacturing process; this should include ease of cleaning and ability to maintain control parameters (including sterilization, if applicable). Test results consistently at or near the upper or lower limits indicate problems with the process or incompatibility with the equipment. All equipment should be adequately identified in each batch record. A detailed description of all equipment should be given in the submission as well. The suitability of the equipment for the process can be determined by a review of the installation and operational qualification reports to ensure that equipment can operate at the ranges specified in the manufacturing procedure.

H. Production Controls and Process

In the review production controls, the proposed production process, which must be manufactured in full compliance with GMPs, should be identical to the process used for the manufacture of the biobatch and the stability batch. Any changes in SOPs, controls, or formulation between test batches and proposed production batches should be justified (i.e., addition of ingredients by automated equipment). For bulk drug substances, a change in solvents may require prior FDA approval if these can be considered a significant change. A review of product annuals will indicate if there are problems with manufacturing or controls (for example, where there have been frequent reworks or failures, and at what percentage). In establishing operating parameters, supporting data are required (retest batches, equipment rating, or characteristics). Time limits should be specified for each phase of processing, including a clear explanation of the starting and end times, where necessary. A detailed sampling plan (showing source and location of each sample) for development batches should be included. In addition, a flow chart of the manufacturing process should be provided.

Batch records for the packaging and labeling of clinical batches should be available and similar in content to those to be used for marketed products.

I. Laboratory Records and Controls

Regarding laboratory controls, a review of laboratory notebooks and chromatograms should be done to check the reliability and authenticity of the supporting data in the methods development and testing of the clinical, bio, and stability batches. Reference standards used should be certified as standards. The FDA expects that, for bulk substances, the suitability of reference standards should be more extensive than that of bulk drug substance specifications. A comparison of analytical methods and specifications for lots of drug substance used in clinical batches and biobatches should be performed to see if any deletions or revisions to any specifications occurred.

One should verify that the method of recordkeeping in the development laboratory follows what is stipulated in the FDA's "Laboratory Inspection Guide," from June 1992. The system should also be evaluated for the transfer of validated analytical methods. "On-site" validation of the method is required for analytical methods validated at another laboratory. A written procedure should be available covering both the transfer of methods and on-site validation and revalidation. When contract laboratories are being used, verification that the laboratory is using the correct analytical methods and specifications should be performed.

J. Validation of Analytical Methods

Concerning validation of analytical methods, all methods must be validated prior to the PAI. The validation should include an approved validation protocol and report. The validation protocol should include:

1. Method of evaluating validation results
2. Acceptance criteria for all analytical parameters

Compendial methods for drug substances generally do not require any additional validation; however, drug products may require some limited validation to demonstrate that the drug matrix does not interfere with the compendial method.

Acceptance by FDA headquarters of specifications in the submission does not necessarily mean the FDA field office will accept them. The FDA field office during the PAI will check for appropriate development data to support filed specifications and ensure that these specifications are realistic. The submitted specifications should be supported with reliable and reproducible data and be sensitive and discriminating so that changes in raw materials or products can be detected.

K. Equipment Cleaning

Regarding cleaning of equipment, a review of the cleaning procedures for the new drug product and assurance that the cleaning procedures have been validated should be undertaken. One should check for possible cross-contamination with highly insoluble or sensitive drugs. Inspection of pipes and hoses and other areas difficult to clean should be considered. A check for validated cleaning procedures in the development area is recommended to determine whether cleaning procedures have been validated against the products manufactured. Cleaning validation includes residue limits and methods of sampling that the FDA expects as achievable and verifiable at the ppm level. The swabbing method is expected to be used with other sampling methods.

L. Process Validation

Equipment qualification and process validation are expected for clinical and biobatches to show batch uniformity and process control. A master validation plan should be available and include the company's philosophy of the matter (what will be validated, who will validate, when and under what conditions will revalidation be undertaken). Full validation of the manufacturing process is not required before a facility receives a PAI. Validation of bulk drugs for each batch size is not required prior to the PAI; however, at minimum a validation protocol should be available. Problems found with a process validation done prior to a PAI does not constitute disapproval; the firm would have the opportunity to correct deficiencies before shipping the new approved drug product. Process validation should include data generated at various operating conditions to bracket the manufacturing parameters and limits. The key to validation of bulk drug substances is proving that the actual production process can consistently operate within the defined critical parameters according to the FDA. Validation studies for bulk substances should include the following:

A flow chart of the process
A discussion concerning the scientific basis for the process, including its limitations and efficiency
A narrative discussion of each step of the synthesis, including what each step accomplishes, its limitations, the quality level of the intermediate produced at each step, and the impurities (if any) generated from each step
The identification of critical steps in the process and how they are monitored and controlled
A discussion of the established parameters for the critical steps and what happens if actual conditions are outside these established parameters
A discussion of any recovery procedures, how they work, and their limitations (for example, to demonstrate that recovered solvent is suitable for its intended use or comparable to virgin solvent)
A discussion of the process refinements to lower impurities
A discussion of the quality and equivalence of product recovered from the mother liquor to the first crop
For reworks, a description of the cause for the process failures that would result in a rework and the contaminants or impurities the rework is intended to remove

M. Master Batch Record

Documentation and recordkeeping of a separate master record with original signatures from the QA or QC departments to indicate their approval should be maintained. A master batch record should not be used as a batch record even if only one batch is to be produced from the master batch record. All manufacturing conditions and equipment usage should be recorded. This information is considered critical to support the proposed scale-up manufacturing process. Investigation reports should be available to address all production problems or difficulties. The batch record for clinical supplies should be a stand-alone document; any references made in the batch record and all supporting documentation should be included as part of the batch record.

For aseptically produced products, a justification for using aseptic processing instead of terminal sterilization should be provided. A batch record for clinical batches should include a specimen label as required by 21 CFR 211.186. Any development batch that failed specifications should include an explanation and a full investigation in accordance with 21 CFR 211.192. Reasoning as to why these batches were not included in the submission should be documented and justified. In review of stability studies, a formal stability program should be available specifying container closure system, storage conditions, test intervals, and parameters. The processing and control parameters used for stability batches should cover limits specified for the proposed production batches. Test batches on stability should be manufactured at the proposed manufacturing site.

Strict accountability for all clinical supplies is important to avoid any suspicion of drug diversion or fraud. Records covering drug returns, distribution, and destruction should be available.

N. Quality Assurance

Quality assurance procedures and controls should be similar to those used for marketed products. Complete and comprehensive follow-up investigations, including a written report, are required for any failures or discrepancies. Any investigation report should at minimum include:

The reason for the investigation
A summation of the process sequences that may have caused the problem
An outline of corrective actions necessary to save the batch and prevent a similar recurrence
A list of other batches and products possibly affected, the results of investigation of these batches and products, and any corrective action.

Specifications or processing parameters should not be changed to accommodate or correct the failure unless there is conclusive evidence that a specific parameter or specification is responsible for the failure.

Where reprocessing is considered, supporting data must be available to show that reprocessing will result in a product equivalent to the original.

O. Development Report

The development report of the drug product is very crucial for a PAI. In narrative form, it should summarize the development process, thereby linking all information and data to demonstrate equivalency of the proposed manufacturing formulation, process, and controls to the clinical trials. A good development report indicates that the applicant has the appropriate level of knowledge and control over the product and manufacturing process. The FDA often uses the development report to identify potential process-related problems or difficulties in technology transfer, which then would be subject to in-depth coverage during the actual PAI. At present, there are no standard industry practice or FDA guidelines regarding development reports. Recent FDA recommendations of the contents for a development report should include the product formulation; manufacturing instructions; laboratory reports; and the rationale and validation for manufacturing processes, raw material specifications, and release parameters. Specifically, the development report should include or be supported by the following available data:

1. The physical and chemical properties necessary to characterize fully the drug substance, which includes, but is not limited to, identification of impurities, particle size, solubility, bulk density, polymorphism, hygroscopicity, etc.
2. The manufacturing procedures used to manufacture development batches, biobatches, and batches used for pivotal clinical studies, which must be specific and well documented
3. Granulation studies (if applicable) to include sieve analysis, bulk density, moisture, blend uniformity, etc.
4. Finished product test results to include content uniformity, assay, hardness, friability, etc.
5. Dissolution profile (at minimum for the biobatch and pivotal clinical batches)
6. Stability

During the PAI, the investigator will review underlying raw data and analytical worksheets to assure the accuracy and reliability of the data reported.

Regarding sterile dosage forms, the additional developmental data needed to support the filed process would include physical factors (extrusion force, particulate levels), metal/light sensitivity, filter compatibility and integrity, oxygen sensitivity, container requirements, preservative effectiveness, heat sensitivity (autoclavability), drug substance (source, chemical, microbial purity), manufacturing procedures and equipment, in-process test data, and final dosage form test results.

The development report should identify critical variables for the process and how to monitor and control these variables during scale-up, as well as show correlation of the production batches with the biobatch and clinical batches. A system for the technology transfer from research and development to production should also be provided, and at minimum an SOP describing such a procedure should be available. The rationale for the formulation should include a discussion of the chosen raw materials. (Raw material inventory records should be available during the PAI, because the investigator will review them to evaluate the quantities of materials used, the testing performed, and the source of the raw material.) A discussion of the equipment used during development, including a comparison of any different pieces of equipment used to manufacture the developmental batches, should be part of the report. It is also important to include the justification and documentation of any deviation from the established manufacturing procedure, as the investigator will look to see what changes were made or what conclusions were drawn, if any, as a result of the deviation. The conclusion of the development report should be a discussion of the consistency of the process, failures (if any), scale-up problems (if any), bioequivalency among batches, and rationale of decisions made as a result of failures and problems.

VII. POST PAI

A PAI, of course, is not statutorily required for approval of an application to market a drug product. A PAI may be requested by FDA headquarters' staff or conducted at the district office's discretion. Generally, if deficiencies are noted, at the conclusion of the PAI, the investigator will provide a letter to the company explaining its decision to recommend that approval be withheld until the center reviews the field's data. There are several layers of review within the Agency after a PAI. The supervisory inspector, branch director, compliance officer, and district director may review any resulting deficiencies in the FDA district office. The FDA headquarters' review will be performed by the Office of Compliance in the Center of Drugs when the district recommends withholding approval of the application. Upon receipt of written certification from the company stating that the noted deficiencies have been corrected, the FDA field office is obligated to clear the application within 45 days if the correction is adequate. In providing responses to deficiencies, a company may have to conduct some additional or repeat tests where the records were lost. On the basis of the data and records that do exist, one may need to obtain a professional's opinion about the data to demonstrate that the lost records will not have a material impact on the product or process. Careful thought and analysis and discussion of the lost records with the Agency are generally the best approach under these situations.

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Quality Assurance

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I. INTRODUCTION

The complexities involved in NDD have increased in the past 5 years. This has occurred as the result of enhanced drug development techniques and global registration attempts. Spurred also by the effort to maximize profits, this phenomenon has placed the Quality process under increased and manifold stress. The QA and QC processes are placed in the forefront by any major drug development organization. The efforts of QA will be reviewed in this chapter.

Any review of the practices involved in defining and describing QA within the NDD process must begin by discussing the scope of QA activities.

For many large-scale pharmaceutical development organizations, QA exists through the complete life cycle of the drug development process. In the United States, the practice of QA is neither required nor defined by a regulatory standard within each of the drug development activities or stages. The assurance of quality *is* expected, however, by regulatory agencies for organizations that attempt to develop and market a new drug entity. In fact, drugs that use devices as the delivery system elevate the expectation for a regulatory base necessary for assurance activities, because in-process audits become a regulatory requirement.[1]

In the far broader scope of NDD and global submissions, global initiatives to introduce a more formal QA program to industry has been well received. As recently as 1996, the ICH[2] has included the activities of QA and QC as separate entities within its guideline for GCP.

Quality assurance associates will generally be using interviews, reviews and audits[3] as the mechanism to determine if the firm is compliant with regulations, current accepted practices (cGCP, cGLP, and cGMP activities), and internal procedures.

Internal written policies and procedures must be developed to define the scope of QA activities within the company. These policies and procedures should encompass those areas within the company that, after an assessment of risk, provide the most assurance that safety and integrity are designed into the drug development process.

Quality assurance should function in a reporting channel independent from the main operational development flow, yet a close working relationship with these same operations personnel should be a priority.

Internal QA procedures generally are sufficient in scope to utilize a thorough sampling process to determine internal operations' effectiveness in completing corporate objectives, policies and procedures.

II. THE QUALITY ASSURANCE DEPARTMENT

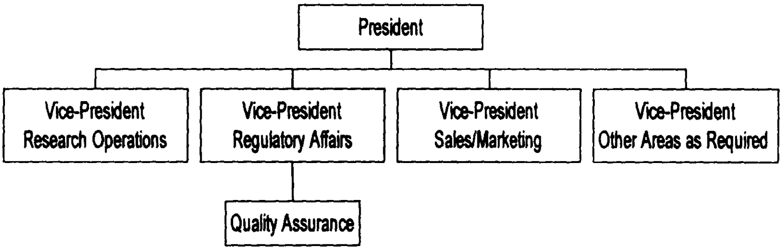
The QA department will usually consist of a group of specialists, each having a high degree of knowledge and many years of experience in drug development. This background allows them to provide practical advice to the drug development departments with which they interact.

Auditors within the QA group usually possess very good cognitive skills, developed over many years within various aspects of the drug development process. They use their knowledge and experience to provide assistance and practical applications and suggestions to departments and colleagues.

Other attributes typically observed with QA associates are refined communication skills, personal integrity, patience, and a penchant for detail.

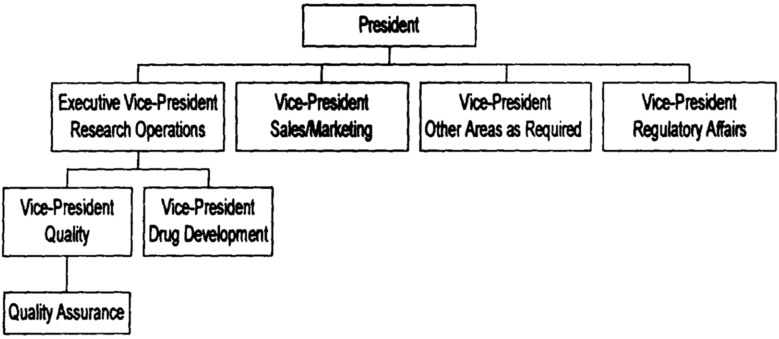
The QA department may reside in a special pathway reporting directly to management. There may be a corporate oversight compliance group, as well as functional groups within each drug development pathway (Scenario 1). This pathway is the more common pathway experienced by drug development firms today.

Corporate Scenario One


President
Vice-President Research Operations
Vice-President Regulatory Affairs
Vice-President Sales/Marketing
Vice-President Other Areas as Required
Quality Assurance

Another scenario may exist in which there may be direct reporting within the research development pathway, yet with such a reporting relationship defined as outside of potential influence (Scenario 2).

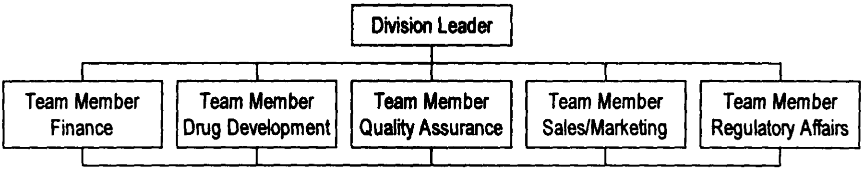
Corporate Scenario Two


President
Executive Vice-President Research Operations
Vice-President Sales/Marketing
Vice-President Other Areas as Required
Vice-President Regulatory Affairs
Vice-President Quality
Vice-President Drug Development
Quality Assurance

In this scenario, key drug development operations are focused under one banner. Peer groups, with similar report structure and supervisors, administer responsibility for corrective and preventative actions.

Indeed, in this nuclear age, a new corporate scenario (Scenario 3) has emerged. This scenario places the focus of responsibility within the team.

Corporate Scenario Three


Division Leader
Team Member Finance
Team Member Drug Development
Team Member Quality Assurance
Team Member Sales/Marketing
Team Member Regulatory Affairs

In this scenario, QA interacts with team members during the drug development process and reports observations to team members for their corrective and preventative action and documentation process.

The preceding three scenarios are only a few of the designs utilized globally by drug development organizations. However QA may fit in the organization, the information supplied by the group can help to identify potential issue areas and compliance failures.

A. Operations within the Quality Assurance Department

Most QA departments use a variety of methodologies to complete their objectives. These methods include discussions (group, individual), document and file reviews, direct examination of records, and indirect audits[4] (which correlate information from various sources to determine procedure compliance for a specific area).

Advance planning with development personnel can begin in many different ways. Typically, a project planning committee defines key stages in a new drug entity's life cycle. The committee will usually include the QA professional as a part of the team, which allows him or her to arrange a plan for monitoring the development life cycle from concept to submission.

A development strategy schedule will define those stages in the development of a new drug entity that require assurance of satisfactory completion. Two sources of information will fuel the decision for the new drug entity to advance satisfactorily to the point of NDA submission. One information pathway is focused on drug development typically called the clinical research department. Through the efforts of this department, case report information is transferred from the investigation site through the data management arm of the company, and turned into cleaned, confirmed data for submission to the appropriate regulatory entity.

Traditionally, reviews and audits may be conducted in one of three ways:

- Only by QA
- Together with the operations department
- With a third party

B. Effective Quality Assurance Can Influence Corporate Outcomes

Quality assurance activities can have a beneficial effect on corporate outcomes. Effective QA can save the firm money by discovering potential problems early in the drug development process, allowing for early institution of corrective measures.

Quality assurance departments that demonstrate a history of effectiveness within the corporate culture and foster loyalty among their peers are usually known for fairness, constructive approach, cooperative attitude and informative style.

In addition, QA can provide valuable assistance to associates by helping them understand their weaknesses in either knowledge or the implementation of regulations or corporate procedures. In some companies, a well-developed pathway from dissemination of information is present, to provide quick feedback to those audited.

Also, QA can assist management by assessing inter-departmental and intra-departmental inconsistencies. This can occur for example, by identifying associates who function inconsistently with other associates or those managers who expand procedures beyond corporate intent.

Periodically, colleagues will operate under different assumptions related to corporate policies and procedures. Quality assurance can provide valuable assistance to management, through immediate feedback, when differences occur in understanding and viewpoint.

Other QA activities that have proved effective in saving resources and costs include: identifying protocol design and protocol implementation flaws; documentation deficiencies; deviations from procedures or regulations by either the sponsor, monitor, investigator or contract firm; and providing gap analysis information to management on training deficiencies.

C. Quality Assurance Activities within the Early Phase of Drug Development

Quality assurance activities actually begin early in the drug development process—in the analytical phase. United States' requirements[5] are established as early as non-clinical laboratory studies. At this early phase, the audit program concentrates on in vivo and in vitro experiments, focusing on early drug entities. These drug entities are tested under laboratory conditions to determine their potential safety risk. At this phase, human subjects (e.g., clinical studies) or field trials in animals are not involved.

Quality assurance efforts within this phase will focus on four types of studies conducted for safety evaluation: (a) safety studies on regulated products, (b) safety studies that encompass the full scope of laboratory operations, (c) studies that are significant to safety assessment, e.g., carcinogenicity, reproduction, chronic toxicity studies, and (d) studies that encompass operations for several species of animals.

At this phase of research development, QA efforts will consider adequacy of management reporting structures for delegation of responsibility (along with appropriate supervision and accountability) and assignment of qualified personnel. Additional areas reviewed by QA include study processes and conduct, documentation measures, QC mechanisms such as management oversight/monitoring and internal training requirements, adequacy of facilities, maintenance and calibration of equipment, and retention of regulatory-required sample procedures.

Additional efforts may be focused by QA for operations' compliance with cGLP regulations and monitoring for compliance with cGLP regulations where appropriate.

Non-GLP studies such as methods development, in vitro biochemical mechanisms and other groups such as chemistry, pathology, microbiology, and food science studies for compliance with requirements may also be audited by QA. Further areas such as automated chemical data systems and analytical methods may also be audited.

D. Phase 1 through Phase 3 Drug Development Activities and QA

The QA programs focused during these phases contain many similar activities. These revolve around confirmation that appropriate regulatory requirements and corporate procedures are carried out by personnel associated with these activities.

Phase 1 through phase 3 areas in which QA reviews or provides audit activities may include the following (including categories generally reviewed):

1. *Institutional Review Committee*

Document review prior to study initiation
Investigator qualifications by a CV
Continuing review of investigation
Financial, coercion/undue influence
Membership
Written procedures

2. *Investigator*

Investigation products
Randomization procedures
Informed consent of trial subjects
Records and reports
Safety reporting
Trial termination or suspension
Qualifications
Agreements
Resources
Medical care of trial subjects
Communication with IRC
Compliance with protocol

3. *Sponsor*

Quality controls
Medical expertise
Trial design

Trial management, data handling, records
Investigator selection
Allocation of responsibilities
Compensation to subjects
Notification to regulatory authorities
Confirmation of review by IRC
Information on investigation products
Manufacturing, packaging, labeling
Supply and handling of products
Record access
Safety information
Adverse drug reaction reporting
Monitoring
Noncompliance reporting
Clinical trial reports
Training and development

4. *Data Management*[6]

Procedures
Document design (e.g. CRF)
Document tracking
CRF correction
Data entry
Data coding
Quality control system
Computer system, software
Data reporting
Record keeping
Record retention
Training initiatives

5. *Regulatory Submissions*

Text consistency, grammar, spelling headers, footers, pagination, and spacing
Compare CRF data points with report
Protocol statements with report statements
Data validity and verification
Appropriate signatures

6. *Compliance with Validation Requirements*

System overview
Validation test environment including hardware, software
System security including passwords, network rights, functional security, physical security, modem access and virus protection
Validation test environment including related documents, along with standard operating procedures, user manuals, and system development/ maintenance and documentation
Validation assumptions, exclusions, and limitations
Responsibilities matrix
Validation data sets
Acceptance criteria
Expected results
Execution of the validation plan
Resolution of errors
Documentation
Training records
Archives, storage, backup, and recovery procedures
Methodology and change control
Disaster, recovery, and contingency planning

7. *Contract Vendors*

Previous experience
Facilities
Affiliations
Qualifications of personnel
Services available
Offered procedures
Capability to complete project
Quality controls program
Quality assurance program
Review and approve contracts
Future compliance audits
Database management
Validation/verification needs
Contract laboratories
Procedures
Facilities/equipment
Personnel qualification
Training
Methodology

8. *Contract Laboratories*

QC program
QA program
Computer validation procedures
Results acceptance procedures
Documentation
Maintenance calibration
Record-keeping/retention
Computer system/software
Specimen handling/storage
Specimen analysis/reporting
Result reporting
Accreditation/licenses
Software system vendors/suppliers
Appropriate understanding of procedures

9. *CROs*

Organization
Staffing/resources
Experience
Controls/assurance
Standard operating procedures
Other items as identified above

III. SUMMARY

The QA function is responsible for assessing the localized accountability for performance by operations, and assisting management in determining the impetus for training needs and measuring consistency among associates. By using audit results in trend analysis statistics, QA provides periodic management compliance review of observations from a procedural viewpoint, assists in determining the need to establish new SOPs, the need to clarify existing SOPs, and the need for new or refresher training. Quality assurance also provides information to management on safety reporting compliance, ethical considerations, delegation of responsibilities, study medication compliance and procedural deficiencies, data problems, administrative documentation issues, and feedback on monitoring issues.

ENDNOTES

[1] FDA Regulation 21 CFR Part 820-Quality system regulation. Source: 61 FR 52654, Oct. 7, 1996, unless otherwise noted

[2] The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

1.0 Definitions

1.46 Quality Assurance (QA). All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

1.47 Quality Control (QC). The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

5.1 Quality Assurance and Quality Control

5.1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

5.1.2 The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see 1.21) to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

5.1.3 Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

5.1.4 Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

5.19 Audit

If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

5.19.1 *Purpose*

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

5.19.2 *Selection and Qualification of Auditors*

(a) The sponsor should appoint individuals, who are independent of the clinical trials/systems, to conduct audits.

(b) The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

5.19.3 *Auditing Procedures*

(a) The sponsor should ensure that the auditing of linical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.

(b) The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).

(c) The observations and findings of the auditor(s) should be documented.

(d) To preserve the independence and value of the audit function, the regulatory authority (ies) should not routinely request the audit reports. Regulatory authority (ies) may seek access to an audit report on a case by case basis when evidence of serious GCP noncompliance exists, or in the course of legal proceedings.

(e) When required by applicable law or regulation, the sponsor should provide an audit certificate.

[3] Audit Definition (ANSI). To conduct an independent review and examination of system records and activities in order to test the adequacy and effectiveness of data security and data integrity procedures, to ensure compliance with established policy and operational procedures, and to recommend any necessary changes.

[4] Direct and indirect audits. There are instances in which an indirect audit will prove of benefit within the organization. Examples of these may be the transition of information from another audit process or source such as drug accountability information from manufacturing's receipt of investigator returns with drug accountability logs and patient compliance information.

Examples of direct audits include:

Adverse event reporting
Operations area process
Management communications
Systems validation

Follow-up to an operations audit
Contractual responsibilities

[5] NonClinical Quality Assurance. Quality assurance unit means any person or organizational element, except the study director, designated by testing facility management to perform the duties relating to quality assurance of nonclinical laboratory studies.

Nonclinical laboratory study means in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety. The term does not include studies utilizing human subjects or clinical studies or field trials in animals. The term does not include basic exploratory studies carried out to determine whether a test article has any potential utility or to determine physical or chemical characteristics of a test article.

[6] International Conference on Harmonization; Guideline on Data Elements for Transmission of Individual Case Safety Reports. This document's efforts focus on quality control/quality assurance endeavors to ensure accuracy and to promote validation in the handling of case safety reports for both preapproval and postapproval periods. It covers both adverse drug reaction and adverse event reports.

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Orphan Drugs

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I. INTRODUCTION

When one hears the word "orphan," it sometimes conjures up something out of a Dickens novel—a picture of a homeless, ragged urchin cowering in a doorway in a cold, deserted alley. Unfortunately, relative to orphan diseases and the drugs to treat them, the metaphor has been all too close to the reality of the situation. Many diseases have gone wanting for treatment simply because it is not economically feasible to develop drugs for them. The Federal government, however, has the means to make it more attractive to develop drugs for this lonesome group of diseases. In 1983, the Orphan Drug Act created much needed changes to provide resources that will develop products to treat diseases and conditions. It has had worldwide impact; orphan drug legislation has been enacted in Japan and is being considered in the European Union (1). Interestingly, although the FDA has an orphan drugs directorate and advisory body, one will not find the term "orphan drugs" in any Act of the United States, even though, as noted below, these entities are covered.

There are several benefits of the Act. First, it provides for the development of drugs for diseases that ordinarily would not generate enough revenue to make it worthwhile for a company, thus benefiting society. Second, it provides tax incentives and product exclusivity to the firms that do provide the drugs. This is important. Currently, there are more than 5,000 rare diseases which, although they affect millions of people, they do not represent significant commercial market opportunity to warrant development by many manufacturers.

Several points should be noted. First, an orphan designation does not provide any immunity from producing a valid NDA. The orphan's NDA will be reviewed as rigorously as any NDA. Second, all orphan-designated drugs must be studied under an IND, which will be reviewed as rigorously as any other IND. If the product provides treatment for a life-threatening disease and warrants accelerated development, like any other product under development it will be treated according to the standards for reviewing such diseases, including review under accelerated development in partnership with the FDA.

It also should be noted that often the disease entities involve such a small population of patients that they do not require manufacture under an NDA; rather, these conditions often are treated under an IND. Filing of such an IND is done with the knowledge of the FDA, and often FDA will note that the IND is granted with their knowledge and acceptance that no new drug application will be filed as a result of the studies performed under the IND. However, this is a unique situation reserved for orphan drugs. Often, there are little resources to pursue a full NDA. Often, the sponsor is unable to create appropriate protocols. As will be discussed, the FDA encourages the writing of special protocols to cover the orphan disease and is willing to help write the protocols and help fund the studies. In addition, once an NDA is filed, there are additional incentives that assist the company who is pursuing an orphan drug application.

In the Food, Drug, and Cosmetic Act of 1938, as amended, the location of what we affectionately refer to as orphan drugs is "Subchapter B—Drugs for Rare Diseases or Conditions." The original parts of the subchapter were added in 1983, with amendments made in 1984 and 1985.

The law gives the following definition:

> The sponsor of a drug for a disease or condition which is rare in the States may request the Secretary to provide written recommendations for the nonclinical and clinical investigations which must be conducted with the drug before it may be approved for such disease or condition under section 505. If the drug is a biological product, it may be licensed for such disease or condition under section 351 of the Public Health Service Act.[2]
>
> The Secretary shall by regulation promulgate procedures for the implementation of subsection (a).

Many products have been developed for rare diseases or conditions since the inception of this law.

II. RECOMMENDATIONS FOR INVESTIGATIONS OF DRUGS FOR RARE DISEASES OR CONDITIONS

In section 525(a), FDA notes that the sponsor of a drug for a disease or condition that is rare may request the Secretary to provide written recommendations for the nonclinical and clinical investigations which must be conducted with the drug before it may be approved for such disease or condition under section 505. This is important, because often the complexity of the disease requires more specialization in protocol writing than the sponsor can muster. In addition, having the FDA help with the protocols will assure speedier review further along in the NDA process.

A. Designation

The Act goes on to describe how a firm can provide proof to the agency that a drug is to be considered for such designation. Section 526(a)(2) states:

> For purposes of paragraph (1), the term "rare disease or condition" means any disease or condition which (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug. Determinations under the preceding sentence with respect to any drug shall be made on the basis of the facts and circumstances as of the date the request for designation of the drug under this subsection is made.

There are a number of caveats that the FDA adds to the mix when approving drugs for rare diseases or conditions. Section 526(b) notes:

> A designation of a drug under subsection (a) shall be subject to the condition that (1) if an application was approved for the drug under section 505(b), a certificate was issued for the drug under section 507, or a license was issued for the drug under section 351 of the Public Health Service Act, the manufacturer of the drug will notify the Secretary of any discontinuance of the production of the drug at least one year before discontinuance, and (2) if an application has not been approved for the drug under section 505(b), a certificate has not been issued for the drug under section 507, or a license has not been issued for the drug under section 351 of the Public Health Service Act and if preclinical investigations or investigations under section 505(i) are being conducted with the drug, the manufacturer or sponsor of the drug will notify the Secretary of any decision to discontinue active pursuit of approval of an application under section 505(b) . . . or approval of a license under section 351 of the Public Health Service Act.

B. Protection for Drugs for Rare Diseases or Conditions

One of the key provisions the FDA worked into the regulations was the protection of the holder of the application. For holders of NDAs that have been approved under these provisions, FDA will grant 7 years market exclusivity. Section 527 of the Act notes:

> Except as provided in subsection (b), if the Secretary—(1) approves an application filed pursuant to section 505(b), (2) issues a certification under section 507 [ed. note, this was repealed in 1997], (3) issues a license under section 351 of the Public Health Service Act for a drug designated under section 526 for a rare disease or condition, the Secretary may not approve another application under section 505(b) . . . or issue another license under section 351 of the Public Health Service Act for such drug for such disease or condition for a person who is not the holder of such approved application. . . . or of such license until the expiration of seven years from the date of the approval of the approved application. . . . or the issuance of the license. Section 505(c)(2) does not apply to the refusal to approve an application under the preceding sentence.

The FDA goes on to note that although there is market exclusivity of 7 years, if the applicant is unable to meet demand, the Secretary may approve another product to meet such demand. Section 527(b) notes:

> If an application filed pursuant to section 505(b) is approved for a drug designated under section 526 for a rare disease or condition . . . or if a license is issued under section 351 of the Public Health Service Act for such a drug, the Secretary may, during the seven-year period beginning on the date of the application approval . . . or of the issuance of the license, approve another application under section 505(b) . . . or issue a license under section 351 of the Public Health Service Act, for such drug for such disease or condition for a person who is not the holder of such approved application . . . or of such license if—(1) The Secretary finds, after providing the holder notice and opportunity for the submission of views, that in such period the holder of the approved application . . . or of the license cannot assure the availability of sufficient quantities of the drug to meet the needs of persons with the disease or condition for which the drug was designated; or (2) such holder provides the Secretary in writing the consent of such holder for the approval of other applications, issuance of other certifications, or the issuance of other licenses before the expiration of such seven-year period.

1. Open Protocols for Investigations of Drugs for Rare Diseases or Conditions

As noted earlier, an IND needs to be filed for any orphan indication. To meet the needs of an NDA, many different types of studies are needed, as noted in other chapters in this book. The FDA specifically encourages the preparation of protocols to study the rare disease and condition preparatory to filing an NDA. Section 528 of the Act states:

> If a drug is designated under section 526 as a drug for a rare disease or condition and if notice of a claimed exemption under section 505(i) or regulations issued thereunder is filed for such drug, the Secretary shall encour-

> age the sponsor of such drug to design protocols for clinical investigations of the drug which may be conducted under the exemption to permit the addition to the investigations of persons with the disease or condition who need the drug to treat the disease or condition and who cannot be satisfactorily treated by available alternative drugs.

To briefly discuss the incentives available to the industry:

1. The sponsor receives 7 years' exclusivity if their NDA remains unique for the product, and if no significant improvements are instituted by a competitor.
2. If requested, the sponsor can have help with protocol assistance from the FDA during development.
3. An orphan product manufacturer is entitled to tax credits up to 50% of qualified clinical research expenses incurred in developing the product. This tax credit was permanently extended by Congress and signed by the President in August of 1997 (3).
4. Researchers may apply for grant funds to support pivotal clinical trials. As noted later on, this may be for up to $200,000 for a phase II or III study.

2. *Steps in Obtaining Orphan Product Designation*

As discussed earlier, the first step in orphan product development is the determination that the product is indeed entitled to orphan designation. The government gives one criterion as a *prevalence* of 200,000 individuals in the United States (not *incidence*). Extensive research into the disease must be conducted. The object of this chapter is not to discuss research techniques; however there are numerous government sources or national foundations that may be enlisted to help research the disease with appropriate demographic data. All such data should be carefully compiled and tabulated for presentation to the government.

Careful analysis must be made to assure proper presentation of the specific aspects of the disease and of the product itself in relation to the disease. Presentation of the product is very important. Sponsors of orphan products that cannot prove their product's individuality in the treatment of the disease might find themselves competing with another similar product, which has also earned an orphan designation.

One thing to remember is that although there may be exclusivity to an orphan product granted an NDA, there is no exclusivity to the orphan designation itself; thus, two competitors may be pursuing an NDA for the same indication. If the products are sufficiently similar, the first one with an NDA will be the one with exclusivity. Unless the competitor can show that his product is unique and different from the other product, he will be denied an NDA. If the two products can be shown to be significantly different from each other, both will be granted an NDA, assuming they both pass the government's scrutiny on review.

With regard to the scope of orphan drug exclusivity, FDA notes the following in 21 CFR 316.31—Scope of orphan-drug exclusive approval:

> (a) After approval of a sponsor's marketing application for a designated orphan-drug product for treatment of the rare disease or condition concerning which orphan-drug designation was granted, FDA will not approve another sponsor's marketing application for the same drug before the expiration of 7 years from the date of such approval as stated in the approval letter from FDA, except that such a marketing application can be approved sooner if, and such time as, any of the following occurs:
>
> (1) Withdrawal of exclusive approval or revocation of orphan-drug designation by FDA under any provision of this part; or
>
> (2) Withdrawal for any reason of the marketing application for the drug in question; or
>
> (3) Consent by the holder of exclusive approval to permit another marketing application to gain approval; or
>
> (4) Failure of the holder of exclusive approval to assure a sufficient quantity of the drug under section 527 of the act and Sec. 316.36.
>
> (b) If a sponsor's marketing application for a drug product is determined not to be approvable because approval is barred under section 527 of the act until the expiration of the period of exclusive marketing of another drug product, FDA will so notify the sponsor in writing.

It should also be noted that if the sponsor receives NDA approval and then is not able to provide sufficient supply, he might lose exclusivity. He can either consent to let other applications be filed, or the director may decide to grant approval to other applications. FDA may withdraw exclusivity even if other applications are not pending. Once withdrawn, exclusive approval may not be reinstated for the drug (4).

There are a number of applications that can be filed in relation to orphan products. The first is a request for orphan drug designation. An institutional sponsor who wishes a designation in order to perform studies in support of an NDA would file one of these. Another is a request for a grant to conduct a clinical study of safety and effectiveness of an orphan product. A corporate sponsor with limited funds, or an investigator who is conducting research into a disease with an orphan designation or which is eligible for an orphan designation, would file this application. A number of products have been approved from trials given grants.

In keeping with section 316.40—Treatment use of a designated orphan drug—prospective investigators seeking to obtain treatment use of designated orphan drugs may do so as provided in 21 CFR 312.24.

3. *Content and Format of a Request for Orphan Drug Designation*

Title 21 of the Code of Federal Regulations, section 316.20, describes the means by which a company can actually file an application for an orphan drug designation. It is in this section that the government indicates that, "More than one sponsor may receive orphan drug designation of the same drug for the same rare disease or condition, but each sponsor seeking orphan drug designation must file a complete request for designation as provided in paragraph (b) of this section."

The regulations require that a permanent resident of the United States must act as the sponsor's agent upon whom service of all processes, notices, orders, decisions, requirements and other communications may be made on behalf of the sponsor. The name of the agent must be provided to: Office of Orphan Products Development (HF-35), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857 (5).

It must also be noted that one may apply for orphan-drug designation at any time in the drug development process prior to the submission of a marketing application for the drug product for the orphan indication. A sponsor may request designation of an already-approved drug product for an unapproved use without regard to whether the prior marketing approval was for an orphan-drug indication (6).

The format of the application is straightforward: (7)

The sponsor must submit two copies of a completed, dated, and signed request for designation that contains the following:

1. A statement that the sponsor requests orphan drug designation for a rare disease or condition, which shall be identified with specificity.
2. The name and address of the sponsor.

    a. The name of the sponsor's primary contact person and/or resident agent
    b. The title, address, and telephone number of the contact person/resident agent
    c. Generic and trade name, if any, of the drug
    d. The name and address of the source of the drug if it is not manufactured by the sponsor

3. A description of the rare disease or condition for which the drug is being or will be investigated, the proposed indication or indications for use of the drug, and the reasons why such therapy is needed.

(Note that it is not necessary in this part to deliver volumes of information. The information provided should be factual and concise. Tabulations of statistical data are helpful in describing the patient demographics. The content of the text should be that of a peer-reviewed journal article, about 30–40 pages at most. If the volume of data is such that a brief presentation is not thought possible, it is suggested that the agency be contacted to discuss with them the acceptability of providing longer presentations.)

4. A description of the drug and a discussion of the scientific rationale for the use of the drug for the rare disease or condition, including all data from nonclinical laboratory studies, clinical investigations, and other relevant data that are available to the sponsor, whether positive, negative, or inconclusive. Copies of pertinent unpublished and published papers are also required.

(Note that if there are massive amounts of nonclinical data to be provided, it is wise to discuss the submission of large numbers of volumes to the orphan product review division. Large volumes of information must be submitted with an IND or NDA. Tabular summaries of data, with comprehensive summaries of data are better suited for the orphan designation application.)

5. If the sponsor of a drug that is otherwise the same as an already-approved orphan drug seeks orphan drug designation for the subsequent drug for the same rare disease or condition, an explanation of why the proposed variation may be clinically superior to the first drug is required.

(This is extremely important. The differences alone will not guarantee that the government will grant another application. One must show definitive superiority. Price is not a consideration, unfortunately, in this aspect. Considerable reduction in adverse experiences, superior availability, superior activity, etc., must be considered a part of this process.)

6. Where a drug is under development for only a subset of persons with a particular disease or condition, a demonstration that the subset is medically plausible.

7. A summary of the regulatory status and marketing history of the drug in the United States and in foreign countries, for example, IND and marketing application status and dispositions, what uses are under investigation and in what countries; for what indication is the drug approved in foreign countries; what adverse regulatory actions have been taken against the drug in any country.

8. Documentation, with appended authoritative references to demonstrate that:

a. The disease or condition for which the drug is intended affects fewer than 200,000 people in the United States or, if the drug is a vaccine, diagnostic drug, or preventive drug, the persons to whom the drug will be administered in the United States are fewer than 200,000 per year as specified in 21 CFR 316.21(b).
b. For a drug intended for diseases or conditions affecting 200,000 or more people, or for a vaccine, diagnostic drug, or preventive

drug to be administered to 200,000 or more persons per year in the United States, there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the United States as specified in section 316.21(c).

9. A statement as to whether the sponsor submitting the request is the real party interested in the development and the intended or actual production and sales of the product.

Any of the information previously provided by the sponsor to FDA under subpart B of 21 CFR may be referenced by specific page or location if it duplicates information required elsewhere in section 316.20.

4. Clinical Studies of Safety and Effectiveness of Orphan Products

One way in which orphan products are made available is for the OPD to support clinical research to determine whether the products are safe and effective. All funded studies are subject to the requirements of the FD&C Act and the corresponding Code of Federal Regulations. The goal is the clinical development of products for use in rare diseases or conditions in which either no current therapy exists or current therapy would be improved. Grants are offered for studies intended to provide data acceptable to the agency that will either result in or substantially contribute to approval of these products. The FDA asks applicants to keep this in mind. It requires an explanation in the "Background and Significance" section of the application of how their proposed study will either facilitate product approval or provide essential data needed for product development.

In fiscal year 1999, grants awarded to support clinical trials on the safety and effectiveness of products for a rare disease or condition were anticipated to be in the range of $11.3 million, of which $8.8 million will be for noncompeting continuation awards. This will leave $2.5 million for funding approximately 10 new applications. Any phase clinical trial is eligible for up to $100,000 in direct costs per year plus applicable indirect costs for up to 3 years. Phase II and III clinical trials are eligible for up to $200,000 in direct costs per year plus applicable indirect costs for up to 3 years. The FDA supports studies covered by this notice under section 301 of the Public Health Service Act. Work plans submitted under the application should comply with "Healthy People 2000," a copy of which may be obtained through the Superintendent of Documents, the Government Printing Office, Washington, DC 20402-9325 (stock no. 017-001-00474-0).

The FDA will consider awarding grants only to support clinical studies for determining whether the products are safe and effective for either premarket approval (devices) or in support of an IND for drugs or biologics. Investigations of approved products to evaluate new orphan indications are also acceptable; however, these are also required to be conducted under an IND or IDE to support a change in official labeling. Studies that are submitted for the larger grants ($200,000) must continue in phase 2 or phase 3 of investigation. Those that are submitted for the smaller grants ($100,000) may be phase 1, 2, or 3. The various phases of clinical investigations are discussed in other chapters in this volume. Annual reports must be made on an annual financial status report (FSR) (SF-269) form. The original and two copies of this report must be submitted to the grants management officer within 90 days of the budget expiration date.

Applications must propose a clinical trial of one therapy for one indication. The applicant must provide supporting evidence that a sufficient quantity of the product to be investigated is available to the applicant in the form needed for the clinical trial. The applicant must also provide supporting evidence that the patient population has been surveyed and that there is reasonable assurance that the necessary number of eligible patients is available for the study. In addition, subjects must provide informed consent, and the studies must be conducted in accordance with GCP under the oversight of a duly constituted IRB.

Applications are accepted at designated times during the year. The announcements for this are published in the *Federal Register*, usually midyear. The most recent version was published in August 1998*; another should be published about the same time in 1999.

Application forms are available from, and completed applications should be submitted to, the Grants Management Officer, Division of Contracts and Procurement Management (HFA-522), Food and Drug Administration, 5600 Fishers Lane, Park Bldg., Room 2129, Rockville, MD 20857, telephone 301-827-7185. Applications hand carried or commercially delivered should be addressed to 5630 Fishers Lane, rm 2129, Rockville, MD 20852.

Applications will be evaluated for responsiveness to the application requirements; those deemed unresponsive will be returned. Responsiveness will be based on the following criteria:

1. The application must propose a clinical trial intended to provide safety or efficacy data of one therapy for one orphan indication. Additionally, there must be an explanation in the "Background and Significance" section of how the proposed study will either facilitate product approval or provide essential data needed for product development.

2. The prevalence, *not incidence*, of population to be served by the product must be fewer than 200,000 individuals in the United States. The applicant should include, in the "Background and Significance" section, a detailed expla-

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*63 FR 41855–41859, August 5, 1998, cf. NB: Names, addresses, and telephone numbers may change.

nation supplemented by authoritative references in support of the prevalence figure. If the product has been designated by FDA as an orphan product for the proposed indication, a statement of that fact will suffice. Diagnostic tests and vaccines will qualify only if the population of intended use is fewer than 200,000 persons per year.

3. The number assigned to the IND/IDE for the proposed study should appear on the front page of the application with the title of the project. Only medical foods not requiring premarket approval are exempt. The IND/IDE must be in active status and in compliance with all regulatory requirements of the FDA at the time of submission of the application. To meet this requirement, the original IND/IDE application, pertinent amendments, and the protocol for the proposed study must have been received by the appropriate FDA reviewing division at least 30 days prior to the due date of the grant application. Studies of already-approved products, evaluating new orphan indications also must have an active IND. Exempt INDs must have their status changed to active to be eligible for this program. If the sponsor of the IND/IDE is other than the principal investigator listed on the application, a letter from the sponsor verifying access to the IND/IDEs required, and both the application's principal investigator and the study protocol must have been submitted to the IND/IDE.
4. The requested budget should be within the limits as stated in the application.
5. Consent and/or assent forms and any additional information to be given to a subject should be included in the grant application.
6. All applicants should follow guidelines specified in the PHS 398 grant application kit.

5. *Scientific/Technical Review Criteria*

To provide the first level of review, the FDA will convene an ad hoc expert panel. The applicant will be apprised of the makeup of the panel and will have the opportunity to discuss its makeup to assure that there will be no one sitting on the panel with a conflict of interest.

The application will be judged on the following scientific and technical merit criteria:

1. The soundness of the rationale for the proposed study.
2. The quality and appropriateness of the study design, including the rationale for the statistical procedures.
3. The statistical justification for the number of patients chosen for the trial, based on the proposed outcome measures and the appropriateness of the statistical procedures to be used in analysis of the results.
4. The adequacy of the evidence that the proposed number of eligible subjects can be recruited in the requested timeframe.

5. The qualifications of the investigator and support staff, and the resources available to them.
6. The adequacy of the justification for the request for financial support.
7. The adequacy of plans for complying with regulations for protection of human subjects.
8. The ability of the applicant to complete the proposed study within both its budget and the time limitations stated in the RFA.

A priority score will be given, based on the scientific and technical review criteria noted above.

6. Submission Requirements

Note: Do not send applications to the Division of Research Grants, National Institutes of Health (NIH). Any application sent to NIH which is sent to FDA by them after the due date will be deemed unresponsive and returned to the applicant. However, instructions for completing the forms can be found on the NIH home page on the Internet at http://www.nih.gov/grants/funding/phs398/phs398.html. Forms may be found at http://www.nih.gov/grants/funding/phs398/forms_toc.html. The FDA *does not* adhere to the page limitations or the type size and line spacing requirements imposed by the NIH on its applications. Applications must be submitted by mail delivery as stated above. The FDA is unable to receive applications through the Internet.

Submission of the application must be on grant application form PHS 398, as noted above. An excellent guide entitled "How to Write a Research Grant Application" has been prepared by the government, and is available on request. The FDA has indicated that guidelines will be maintained and a request for the list or for any guideline should be directed to the Office of Orphan Products Development (HF 35), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857 (8).

7. FDA Review and Actions

FDA will review the applications and make recommendations as to the completeness of the submission and what else may be needed.

In section 316.12, Providing written recommendations, FDA notes:

> (a) FDA will provide the sponsor with written recommendations concerning the nonclinical laboratory studies and clinical investigations necessary for approval of a marketing application if none of the reasons described in Sec. 316.14 for refusing to do so applies.
>
> (b) When a sponsor seeks written recommendations at a stage of drug development at which advice on any clinical investigations, or on particular investigations would be premature, FDA's response may be limited to written recommendations concerning only nonclinical laboratory studies, or

> only certain of the clinical studies (e.g., Phase 1 studies as described in Sec 312.21 of this chapter). Prior to providing written recommendations for the clinical investigations required to achieve marketing approval, FDA may require that the results of the nonclinical laboratory studies or completed early clinical studies be submitted to FDA for agency review.

As noted above, FDA may refuse to provide written recommendations for various reasons, such as incompleteness or absence of required information in section 316.10(b). Insufficient information about the drug to identify the active moiety and its physical and chemical properties are cause for refusal to provide recommendations as is, insufficient evidence that the disease is indeed of sufficient incidence to warrant orphan designation, among others. Such refusal will be in writing. The FDA will describe the information or material it requires or the conditions the sponsor must meet for FDA to provide recommendations (9).

Once an orphan designation is granted, it is transferable, provided the owner of the designation informs the FDA in writing of the name of the transferee, and what rights to the designation have been transferred (not all rights need to be transferred). In addition, the new owner must submit a letter accepting orphan drug designation and the date the change is effective, stating that he or she has a complete copy of the request for orphan designation including amendments and supplements and all relevant correspondence. A list of the rights assigned should also be provided. The new owner of the designation should provide a new contact name, including a United States' agent if the new owner is a foreign company. The FDA notes that no sponsor may relieve itself of responsibilities under the ODA by assigning rights to another without assuring that the sponsor will carry out its responsibilities, or without obtaining prior permission from FDA (10).

As with other submissions to FDA, the recipient of orphan designation must provide a report to the FDA within 14 months and annually thereafter until marketing approval to indicate progress, stated in 21 CFR 316.30 as follows:

> (a) A short account of the progress of drug development including a review of preclinical and clinical studies initiated, ongoing, and completed and a short summary of the status or results of such studies.
> (b) A description of the investigational plan for the coming year, as well as any anticipated difficulties in development, testing, and marketing; and
> (c) A brief discussion of any changes that may affect the orphan-drug status of the product. For example, for products nearing the end of the approval process, sponsors should discuss any disparity between the probable marketing indication and the designated indication as related to the need for an amendment to the orphan-drug designation pursuant to Sec. 316.26.

The FDA will not publicly disclose the existence of a request for orphan designation, but there are certain conditions that apply, including whether the sponsor has made it publicly known he has orphan designation. The FDA will determine whether the disclosure can be made in accordance with confidentiality requirements of INDAs and NDAs. Once public availability eligibility has been determined, FDA will publish a list in accord with part 20 and section 314.430 of the CFR and other applicable statutes and regulations (11).

III. FINAL NOTES

To recap, to receive an orphan drug designation for a product, a sponsor must file an application (two copies) with the FDA, according to the prescribed format in 21 CFR 316.20. If the disease affects fewer than 200,000 persons per year (or, in the case of a vaccine, the administration will be to fewer than 200,000 persons per year), the agency may grant an orphan designation. Once so designated, a proper INDA must be filed, which will need to contain a full description of the product, its synthesis and method of manufacture as a drug product, its preclinical pharmacology and toxicology, and clinical protocols for the studies to be conducted. If the sponsor is unable to write the protocols, the FDA will assist in the writing and will even fund the studies if the sponsor has insufficient funds. Orphan designation is assignable, provided the sponsor assures that the new owner will act responsibly in developing the drug. If an NDA is filed and approved, there will be 7 years of market exclusivity granted, as well as tax benefits. The biggest benefit is to the patients who receive much needed help in the treatment of their disease.

REFERENCES

1. Haffner, ME. Orphan drug development—International program and study design issues. Drug Information Journal, Vol. 32, pp. 93–99, 1998.
2. Federal Food, Drug and Cosmetic Act of 1938, as Amended.
3. 26 CFR 1.28-1. (These are the IRS regulations on rare disease research tax credit).
4. 21 CFR 316.36 Insufficient quantities of orphan drugs.
5. 21 CFR 316.22. Permanent-resident agent for foreign sponsor.
6. 21 CFR 316.23. Timing of requests for orphan-drug designation.
7. 21 CFR 316.10. Content and format of a request for written recommendations.
8. 21 CFR 316.50. Guidelines.
9. 21 CFR 316.14. Refusal to provide written recommendations.
10. 21 CFR 316.27. Change in ownership of orphan-drug designation.
11. 21 CFR 316.52. Availability for public disclosure of data and information in requests.

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Clinical Development, Regulations, and Trends for OTC Drugs

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I. INTRODUCTION

Medications purchased without prescription have always played a large role in the health care of Americans, and because today's consumers increasingly demonstrate that they want to "take charge" of their own medical care, the role of OTC medications can only become more important. In addition to the familiar analgesics, antiseptics, and cold remedies, products are now available for self diagnosis of pregnancy and pathologic conditions such as blood in the stool. Consumers seem eager to use them and have embraced the concept of "self care." Various prescription products have been—and others soon will be—switched to OTC status. Thus, it is worthwhile for professionals to become familiar with the mechanisms by which the FDA attempts to ensure the safety of these products, their efficacy for the intended purpose, and their safe use by consumers who do not benefit from the advice of physicians regarding either the diagnosis or the selection and administration of the drug.

II. BACKGROUND

Even though physicians did not often supervise and safeguard the consumers of patent medicines and other pharmaceutical products offered for sale in the early years of this century, the Pure Food and Drug Act of 1906 was not intended to require that these products be either safe or effective. This law required only that the labeling on the package be accurate. The first case tried under this law dealt with an acetanilid pain reliever that represented itself as a "cure" for headaches, the legal issue under dispute being the propriety of the word "cure." Under this law, worthless and dangerous drugs could still be sold, as long as they did not make false claims. Manufacturers were still allowed to sell a "consumption medicine," but they could no longer misrepresent it as a "consumption cure."

The law did not require that drugs be safe until 1938, after the "elixir sulfanilamide" tragedy. A company wishing to make a liquid dosage of sulfa drugs hired a chemist who formulated the product using an ethylene glycol vehicle without considering the toxicity of the liquid. More than 100 deaths, most of them children, were due to ingestion of this toxic compound. Although the formulation was clearly lethal, the only grounds for government action was the fact that the bottles were labeled "elixir sulfanilamide" and the definition of "elixir" required an ethanol solution. This tragedy spurred Congress to pass the 1938 Food, Drug, and Cosmetic Act requiring that new drugs be proven safe for human use before they could be sold.

The requirement that drugs be both effective and safe did not become law until 1962. The Kefauver-Harris amendment to the Food, Drug, and Cosmetic Act passed in 1962 required the FDA to review all drugs released after 1938 for effectiveness as well as safety. This program established the Drug Efficacy Study Implementation (DESI) and the job was assigned to the National Academy of Sciences—National Research Council, which reviewed the data presented for each drug that had been submitted to the FDA.

Drugs were categorized as "effective," "probably effective," "possibly effective," and "ineffective" on the basis of the quality of supporting studies. The last three categories were grouped under the heading "less than effective," and the manufacturers and marketers of drugs with "less than effective" ratings were given an opportunity to present new evidence of efficacy. If the evidence was not satisfactory, the product would have to be withdrawn.

It is worth noting that under the definition of "effective" as applied, all components of a combination product must contribute to the drug's labeled indications. Thus, an appetite suppressant might be demonstrated to be "effective" as an aid to weight loss, but if the same appetite suppressant were mixed with vitamins as a protection against the effects of eating less, the product would be labeled "ineffective," as the vitamins had no role in weight reduction.

The National Academy of Sciences review was a massive job, covering more than 4,500 prescription products and more than 500 OTC products. As the study neared conclusion, there was a further effort to examine the OTC market.

III. THE OTC PROBLEM

Reviewing the OTC preparations represented a unique challenge to the FDA. Although the prescription drug review had encompassed thousands of marketed drugs, the OTC list comprised hundreds of thousands of products. Whereas each prescription drug might be marketed by only one or two firms, a single OTC drug entity might be available under hundreds of brand names and in thousands of combination formulations. There were more than a quarter of a million OTC drug products, but examination revealed that fewer than a thousand key ingredients were used in the formulations. As a result, the FDA elected to review only the active ingredients, not the finished products. The review methodology developed at that time is still in use for ongoing review of new OTC drugs.

A. Phase 1—The Advisory Panel

Over-the-counter products are reviewed in a three-tiered system. The first tier is an advisory panel, composed of a group of scientific voting members representing the disciplines of medicine, pharmacy, pharmacology, toxicology, or other appropriate fields of study. Additional nonvoting members may participate, representing consumer or business interests. The panels are charged with reviewing the active ingredients used in OTC specialty products and grouping them into one of three categories:

Category I.	Generally recognized as safe and effective for the claimed therapeutic indication
Category II.	Not generally recognized as safe and effective, or unacceptable for the claimed indication
Category III.	Insufficient data available to permit final classification

What should be recognized is that these panels, which have included more than 300 participants, are not held to the same scientific standards that would be applicable to an NDA. Although much of the review process is based on scientific data accumulated by the drug manufacturers or past researchers, the panelists are free to rely on their own clinical experience and on uncontrolled trials. Although testimonials and isolated case reports are officially excluded from the evaluation process, the permissible data still allow a great degree of subjectivity to enter into the deliberations. For example, the OTC diet aid decision was made on the basis of two flawed studies that would have been considered questionable if submitted in support of a prescription drug. As will be demonstrated in other areas of this discussion, decisions made with regard to OTC drugs do have a subjective element, and the FDA is, as it must be, responsive to professional and public opinion.

The advisory panels present their findings to the FDA. These reports are summarized in the *Federal Register* as "advance notices of proposed rulemaking." As each proposal is published, interested parties are given an opportunity to comment on the proposed rules. Instructions for submitting comments are provided in the *Federal Register*, including the address to which comments should be sent, and the deadline for submission. Interested parties should make every effort to comment at this point, because the advance notice, although significant, represents only the opinion of the advisory panel and may still be subject to modification. The advisory panel report represents what is considered to be the informed scientific opinion on a given drug. This opinion, however, is subject to review based on further scientific data, whereas proposed rules may be reconsidered on the basis of social, economic, and public policy considerations.

B. Phase 2—FDA Review

The *Federal Register* advance notice is a preliminary notice, offering opportunity for comment and submission of new data for consideration. When all comments have been collected and evaluated, the FDA publishes a rule, also termed a "tentative final monograph." This publication incorporates all changes that were made on the basis of the results of the first publication. There is a review of comments made and a summary of the basis for decisions regarding these comments. That is, the FDA prints a review of the nature of the comments or objections that were filed in response to the first notice and is obligated to respond to these comments. This should be carefully studied, because it reflects both the scientific viewpoint of the advisory panel and the FDA policy decisions.

The publication of the tentative final monograph also provides further opportunities for submission of more data, additional comments and objections, or requests for a hearing with the Commissioner of Food and Drugs. Again, full instructions for submitting comments are provided at the end of the *Federal Register* entry.

This phase comprises publication of those drugs that may be marketed for specific indications, and also "nonmonographs," which describe drugs or indications for which no claims can be made. For example, the advisory panel on aphrodisiacs failed to find any products that could be recommended for that therapeutic claim, and regulations barring the offering of products for a specified indication fall under the "nonmonograph" classification.

C. Phase 3—The Final Monograph

The final stage of the FDA's OTC review is publication of the monograph in its final form. Normally, the monograph is published in the *Federal Register* with a notice that the applicable regulation will go into effect 1 year after the date of publication. After that time, the monograph is incorporated into the CFR. Upon publication in the CFR, the monograph is a formal regulation with the force of law. Although such regulation authorizes any drug manufacturer to market an OTC product using the listed ingredient for the indications that have been approved without the requirement of an NDA submission, it limits any other claims that the marketer may choose to make. For example, a company selling aspirin may freely offer the drug as an analgesic and antipyretic without obtaining specific FDA approval, but the monograph equally bars the company from offering aspirin to consumers for the prevention of myocardial infarction (see "Monograph Labeling," below).

If, after the monograph has been published, a company wishes to market an OTC product in an unapproved formulation or for a purpose that has not been included in the monograph, there are two options open: (a) the firm can offer data to justify revision of the final monograph for the purpose of including previously unapproved formulations or indications, or (b) the company may submit an NDA.

IV. MONOGRAPH GENERAL PROVISIONS

The first section of each OTC drug monograph comprises the general provisions, which are applicable to all OTC drugs whatever their form, content, or intended use. These are general rules regarding manufacturing practices and registration procedures. The general provisions have been less stringent than accepted industrial practice. For example, although the current general provisions require labeling of only the active ingredients in a formulation, the Nonprescription Drug Manufacturers Association has accepted a voluntary rule calling for labeling of all components of a formulation: active drugs, bulking agents, flavors, dyes, and fragrances. This practice helps assure the safety of those who may be allergic to chemicals that are otherwise considered nontoxic.

V. MONOGRAPH ACTIVE INGREDIENTS

The active ingredients section of the monograph lists the acceptable materials for a given therapeutic claim and even goes so far as to specify what other drugs they can be mixed with and how many other components may be placed in the mixture. This applies to mixtures of drugs with the same function as well as to those with unrelated uses, that is, drugs from different monographs. In a typical example, a cold remedy may include an analgesic/antipyretic, an antihistamine, a decongestant, an antitussive, and an antacid. This section would list permissible combinations.

Unlike the prescription drug requirements that insisted that every agent in a combination work toward the same end, OTCs offer a greater degree of liberality, as long as a collection of symptoms, as in the example above, may reasonably be found together. Similarly, under some circumstances, components that are truly ineffective may be permitted in a formulation as long as no therapeutic claims are made for them.

This is a critical distinction from the viewpoint of the OTC manufacturer. During the time of the initial review, many marketed OTC products were found to be ineffective on the basis of the lack of any effective ingredient. Manufacturers were given the opportunity to reformulate these products by adding an effective ingredient to their initial formulation, thereby preserving their market share. Diet aids that contained sodium carboxymethylcellulose (CMC) or other bulking agents were found to be of no value as adjuncts to a weight reduction program, but if the category I agent phenylpropanolamine was added to a sodium CMC capsule, the commercial product need not be withdrawn.

VI. MONOGRAPH LABELING

The labeling section of the monograph specifies what must be placed on a product label: dose, directions for use, warnings, and all other information deemed essential for safe use by the general public. These labeling provisions must be combined with those label requirements already specified under "general provisions."

The labeling section may contain both labeling provisions for the general public and those for professional use. As noted above, the analgesic monograph prohibits promotion of aspirin to the public at large for prevention of myocardial infarcts, but this same indication is contained in the professional labeling. The OTC labeling for ibuprofen limits doses to those with analgesic effects; the professional labeling contains doses with anti-inflammatory action.

Labeling of a product refers to all aspects of packaging, including both the physical label and the outer wrap and included packaging. Whereas prescription labels contain minimal patient information, because the use of the drug is expected to be carried out under professional oversight, OTC labels must provide adequate information to permit safe use of the drug by an untrained person. The normal packaging of an OTC preparation, whether through FDA regulation or general agreement by manufacturers' associations, will contain the following information:

1. *Tamper resistant closure*, appropriate to the type of product.
2. *Description of tamper resistant closure*, a written statement describing the closure. This alerts and informs the buyer how to recognize when the product may have been tampered with.
3. *Product name and statement of identity*, the name by which the product is identified (brand name or generic name) and a brief statement of its intended therapeutic purpose.
4. *Active ingredients*, required.
5. *Inactive ingredients*, which is voluntary but is highly recommended for the protection of individuals who may have allergies or other forms of intolerance.
6. *Indications for use*, a concise statement regarding the purposes for which the drug may be properly used.
7. *Directions and dosage*, which provides full dosage information including dose interval, pediatric dose information, or appropriate warnings against use in young children.
8. *Warnings*, a full statement of the precautions to be taken while using the drug: directions in case of overdose, possible drug-drug or drug-food interactions, adverse effects, and other appropriate cautions. This section may also contain notes about the symptoms being treated (for example, there will be warnings that if symptoms persist beyond a specified period, a physician should be consulted). Some of these warnings, as noted, will be present on all or almost all marketed drugs; others are specific to a single product or class of products.
9. *Expiration date and manufacturer's lot number.*
10. *Name and address of manufacturer or distributor.*

The FDA monograph contains examples of appropriate labeling, and the FDA recommends, but does not demand, that manufacturers use only the precise labeling and wording provided in the monograph. Use of this wording assures that consumers will receive accurate, balanced information about the drug and its intended and safe use. The FDA wording may be preceded with the word "approved" and may be attributed to the FDA. The FDA encourages consumers to look for this wording as an assurance that the information provided is clear and factual.

Manufacturers may use alternative wording on package labels and labeling, but the format must not imply that this wording is "approved" by the FDA. Such alternative wording may be used either alone or in conjunction with the FDA-approved labeling. For example, the manufacturer may have a boxed notice with "Approved indications . . . " and add its own statements outside of the box. This option might be chosen if the manufacturer feels that there is some lack of clarity or potential for misunderstanding in the FDA wording. The manufacturer's statements must be truthful and must conform to the information given in the monograph. Alternatively, the manufacturer may dispense with the FDA wording as long as all statements are truthful and cover the same ground as the FDA-approved statements. Manufacturers who elect to use their own wording may be required to demonstrate the truthfulness of these statements and to show that they provide the same level of protection and information as the words selected by the FDA. If the content of the labeling deviates from the standards set by the FDA, by a change in the dose level or an implication that the drug may be used for some purpose other than that specified in the FDA monograph, or is found in any way to deviate from the limits set by the monograph except in selection of words, then the product would be reclassified as a "new drug" and an NDA submission would be required.

VII. MONOGRAPH TESTING

The testing section of the monograph sets a series of limits on OTC products, including minimum levels of activity for many ingredients. At one time, products might be formulated with a collection of medicaments that spanned the pages of the pharmacopoeia, allowing unscrupulous manufacturers to claim that their formulation had more medicines than any other, and even claim the therapeutic benefits of an ingredient that was present in no more than homeopathic amounts. The test section of the monograph is designed to assure that products are present in sufficient quantities to have the claimed effect, and that they are bioavailable and active. Under the dentifrice section, the monograph sets tests to assure that the fluoride in toothpaste is actually taken into the dental enamel, whereas the antacid section stipulates both the acid neutralizing capacity of the final product and, for combination products, the effects of each component antacid.

VIII. THE NONMONOGRAPH

Nonmonographs, as previously noted, are FDA notices banning the sale of specific products, or the sale of products for specific indications. These prohibitions may be based on toxicity data for specific drug entities, lack of efficacy data for given indications, or other considerations that make distribution of a drug or class of drugs contrary to the public interest. One example was the ban on the sale of camphorated oil, which serves as both an illustration of the nonmonograph and the nature of FDA responsiveness to individual or collective opinion.

Camphorated oil was a traditional counter-irritant preparation, perhaps best known from the old song "John Brown's Baby." Although the preparation was thought to be safe and effective for the uses indicated, it was but one of many products with similar actions and uses, and offered some significant risks of toxicity if it was confused with other fixed oils intended for oral ingestion. Mr. Carmine Varrano, a pharmacist from New Jersey, launched a one-man crusade against this product, presenting reports of incidents in which camphorated oil was ingested in place of castor or cod liver oil. Although Mr. Varrano's efforts were essentially his alone, he was able to convince FDA officials of the validity of his cause, with the result that a nonmonograph was published barring the sale of camphorated oil.

In addition to the nonmonograph for camphorated oil, and for aphrodisiacs as noted above, the FDA has published a nonmonograph for hair restorers. No OTC product may be offered for reversal of androgenetic baldness. Just as the monograph specifies what products may be offered for OTC sale, the nonmonograph clearly defines what products may not be offered and what claims may not be made. Again, preliminary publication of a nonmonograph is subject to review and appeal in the same manner that a preliminary notice is.

IX. REVIEW OF FIVE GLOBAL Rx-TO-OTC SWITCH TRENDS

There is absolutely no doubt that tomorrow's drugs will be better than today's. With the revolution in drug development, in part due to such technologic breakthroughs as recombinant DNA research, drugs are being developed with a far greater specificity of purpose and a deeper understanding of the impact on the human body. They are also becoming much safer to use by the general population.

Is there going to be a cleaning out of the current OTC medicine cabinet around the world as more and better prescription (Rx) products are switched to OTC status and become available to the general public? What is happening overall and how has the general switch scene changed in recent years, especially with regard to the responsible expansion of OTC and self medication (which is one of the goals of SWITCH)?

The OTC industry is changing, sometimes imperceptibly, sometimes very visibly. This section will address five megatrends of Rx-to-OTC switches.

A. The Five Megatrends of Rx-to-OTC Switches

1. Dual status and the growing importance of starting switch planning at Phase 3 or earlier
2. The slower pace of switches today but the greater power of future switched products

3. The aging of the population and how it will affect switches
4. Industry consolidation and how it might impact switches
5. Over-the-counter reimbursement of Rx-to-OTC switched products

Trend 1: Dual Status and the Growing Importance of Starting at Phase 3

We predict that Dual Regulatory Status (DRS) will become the typical *strategy of the future for a vast number of current and future Rx pharmaceutical products in the United States. Moreover, this effort will have substantial spillover and affect non-U.S. markets because of the need to amortize the extra costs to achieve dual status.*

We believe this is a result of two factors: (a) the increased use of direct-to-consumer advertising on prescription products, and (b) the growing role of the "self recognition" concept. Dual status is defined as simultaneous existence of the same molecule in both the Rx and the OTC market. For example, the same Rx molecule may have a higher strength or different indication from its OTC brother. Dual status redefines the shape of the switch; it is a switch that also assumes the continuation of patent protection for the Rx product and perhaps the OTC product also. The correct alternative needs to be mapped out, and sales and earnings need to be established for the various scenarios (Figure 1).

	Early Research/ Preclinical Testing	**Clinical Trials**				
		Phase 1	**Phase 2**	**Phase 3**	**FDA**	**Phase 4**
Years	6.5	1.5	2.0	3.5	1.5	Additional post-marketing testing required by FDA
Test Population	Laboratory and animal studies	20 to 80 healthy volunteers	100 to 300 patient volunteers	1,000 to 3,000 patient volunteers	Review process/ approval	
Purpose	Assess safety and biological activity	Determine safety and dosage	Evaluate effectiveness, look for side effects	Confirm effectiveness, monitor adverse reactions from long-term use		
Success Rate	5,000 compounds		5 enter trials		1 approved	
Timeline	0 Years	6.5 Years	8.0 Years	10.0 Years	13.5 Years	15.0 Years

Figure 1. Drug development and approval process. © Francesco International.

As recently as 3 years ago, virtually no pharmaceutical company was starting switch planning or establishing scenarios at phase 3 or before. The prevailing practice was to address the issue much later (if at all). Now more companies (although by no means all) are at least willing to address the issue around phase III. The implications of that are important. The most essential is that dual status is being considered, along with a pure switch. However, many companies still do not plan for switches. Moreover, many companies that are going to have dual status products as competition are ignoring this trend. One company was unaware and, therefore, unprepared for the dual status of nonsedating antihistamines. That business franchise is guaranteed to have a rude awakening.

As can be seen in Figure 2, we have identified a situation that will become all too frequent in the future for pharmaceutical companies. That is the decision on whether to:

1. Never switch the molecule (base case)
2. Switch only at the end of the lifecycle (pure switch)
3. Have a dual status switch, having different Rx and OTC indications or strengths.

What our chart demonstrates is that if one product jumps to the OTC sector, then the most profitable strategy is the one with dual status, because Rx category profitability will decline given the OTC opportunity.

The growth in the United States of direct-to-consumer advertising and its likely spread to other markets over time increases costs. This new marketing

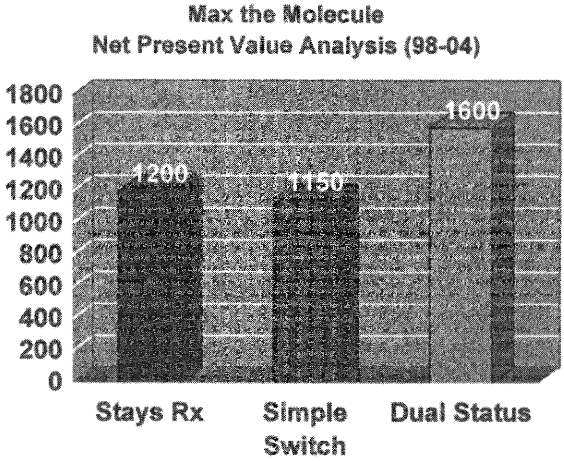

Figure 2. Switch Strategy Financial Comparisons. © Francesco International.

reality will further drive the need to gain added revenue from such strategies as dual status.

Trend 2: A Slower Pace of Switches Today but the Greater Power of Switched Products Tomorrow

The idea that phase 3 is the correct starting place for planning a switch means that literally "the sooner the better" is a key trend to increase chances for success. If sooner is better, then logically another key trend is the following: the more genuine early participation by the research scientists, the better the switched product years later.

It has always been understood by the Rx divisions that quality research division efforts have been at the heart of each successful pharmaceutical company. The feeling that research would be involved in possible switched products was considered wasteful just a few years ago. It represented a diversion of effort away from basic research. Today, the thinking seems to be changing. Numerous companies have taken the longer-term view and are allocating research time against switch issues. The effort is paying off. The successful attack of Pepcid® is largely due to its success in gaining a "prevention" claim against heartburn. That was an idea coming out of a scientific mind. Johnson & Johnson • Merck has sold millions more Pepcid because of this idea, which separated Pepcid from all of the other H_2 antagonists and created the impression that it is different and better (Table 1).

The easy switches have been done. More is still to be accomplished, but as can be seen in Table 2, a lot of products have been switched. The United Kingdom is the leader, yet for 1997 there were no switches at all. There is little doubt that the United Kingdom's future switches will have some very special

Table 1 Number of Rx-to-OTC Switches Comparison* between 1995 and 1998 in Major Markets

	Number of Switches by Country							
Year	US	UK	Canada	Germany	France	Australia	Japan	Total
1995	6	5	2	2	0	3	3	21
1996	4	3	1	7	5	0	0	20
1997	3	0	5	6	3	0	4	21
1998	0	3	5	6	3	0	4	21

*Molecule switches only; for example, nicotine patches are grouped as one. Over-the-counter defined as products free to purchase without a prescription and advertised to the public. Source: SWITCH Newsletter.

Table 2 Switches from Prescription to Nonprescription Status (as of July 1998)

Country	No. of Substances
United Kingdom	92
Germany	82
Canada	81
Mexico	77
United States	62
Spain	56
France	53

Source: SWITCH Newsletter.

circumstances attached to them. Osteoporosis switches and cholesterol switches are not far away.

In the way we are defining OTC—health care products that have an Rx origin—it is certain that OTC has a great future, simply because of the increased scientific attention being given to potential switches. That will be particularly true in areas that have the greatest potential sales volume, such as osteoporosis, cholesterol, obesity, and other areas expected to increase because of the aging of the population.

Trend 3: The Aging of the Population

Significant demographic shifts are taking place in the major markets. The baby boomers (those born after World War II, between 1946 and 1964) are getting older, and their health care needs will be changing accordingly.

In Europe, the population older than age 60 will rise by 18% between 1995 and 2010. In the United States, the population 45 to 64 years of age will increase from 19% now to 26% in 2010, an increase of 37%.

The reasons for this historic change are largely due to two causes: low birth rates and increased longevity. In most of the major markets we cover, the average family size barely duplicates the existing population. The growth in the United States' population (Table 3) is almost entirely explained by immigration into the country. Moreover, the average life expectancy for both men and women has increased dramatically in the last 20 years. In the United States, men are expected to live until age 72 and women to age 79.

With the increasing importance of the 45–64-year-old population segment, a sound marketing company will make adjustments to accommodate this population's health care needs. For the OTC industry, the drug needs and uses of this group will change.

It is worth noting that the 45–64-year-olds have distinctive buying patterns. For example, older consumers:

Are more price conscious
Have more time to make a purchase decision
Are more likely to take prescribed drugs
Have needs different from younger consumers
May have difficulty opening bottles and swallowing tablets

It is important that, although this group may reluctantly accept getting older, they do not want to look and feel older. Therefore, antiaging products promising a younger appearance will be important. These include skin preparations with antioxidants, vitamins such as vitamin C that purportedly have antioxidant powers, and hair restorers, such as minoxidil. In the last 2 years, we have already seen growth in such unusual areas as hair coloring for men. With regard to aging, other categories most likely to benefit are laxatives for irregularity and analgesics for various aches and pains, including arthritis and rheumatism.

Table 3 United States Aging Trend 1998–2020 (Population in Millions)

	Population in Millions by Age Interval										
Year	0–4	5–13	14–17	18–24	25–34	35–44	45–54	55–64	65–74	75+	Total Pop.
1998	20.2	34.3	14.6	25.5	41.7	42.2	30.2	21.2	19.0	14.7	263
2000	19.4	36.5	15.8	25.9	38.2	45.1	36.2	23.7	18.6	16.8	276
2005	19.3	36.8	16.9	28.2	36.8	43.1	41.2	28.9	18.6	18.3	288
2010	20.0	36.2	17.4	30.2	38.2	39.7	44.1	34.6	21.0	19.1	300
2015	21.1	36.9	17.0	31.3	41.1	38.2	42.1	39.4	25.7	20.1	313
2020	22.0	38.7	17.1	30.5	43.6	39.7	38.9	42.3	30.9	22.4	326

Trend 4: Industry Consolidation and How It Might Impact Switches

There is not yet any correlation between launching one OTC switch success and having another success. Being bigger does not necessarily translate into being better at switching.

As can be seen in Table 4, there has been very little change between 1996 and 1997 in the relative ranking of the top 20 companies in the self-medication area. Except, perhaps, for Johnson & Johnson, all who have switched in the recent past have had switch failures.

The reality, at least at present, is that each switch must be judged on its own merits. As stated in trend 1, we have seen the level of sophistication on switching improve dramatically in the past 2 years.

Table 4 Top 20 Companies in the Global Self-Medication Market (Ranked by US Dollar Sales at Manufacturers' Selling Price)

Rank 1997	Rank 1996	Company
1	1	Johnson & Johnson
2	2	American Home Products
3	3	SmithKline Beecham
4	4	Warner-Lambert
5	5	Bayer
6	7	Procter & Gamble
7	6	Novartis
8	8	Taisho
9	9	Bristol-Myers Squibb
10	10	Roche
11	13	Boehringer Ingelheim
12	12	Takeda
13	14	Schering-Plough
14	11	Rhone-Poulenc Rorer
15	16	Pfizer
16	20	Nestle
17	17	Pharmacia & Upjohn
18	—	Hoechst
19	15	SS Pharmaceuticals
20	18	E. Merck

Source: IMSSelf-Medication.

Over-the-counter markets are currently undeveloped in comparison to their Rx parents, as can be seen in Table 5. Therefore, the stronger the Rx product research, the greater likelihood of a solid OTC opportunity. Drug researchers today are eager to produce drugs for a wider range of diseases. The best future comes from the best research. Although it is fashionable to ridicule "big pharma" companies for being too slow, their commitment to their own research is sincere and backed up by billions of dollars. We predict that future switch activity will become dominated by the big companies and that their success rate will improve because the drugs are so superior to what is available today.

Trend 5: OTC Reimbursement of Rx-to-OTC Switched Products

Over-the-counter is basically a derivative business, because it gets many of its products and other business characteristics from its Rx heritage. It is reasonable

Table 5 Over-the-Counter Market Size (As a Percent of the Total Pharmaceutical Market)

OTC Percent of Total Pharmacy Market by Country			
Country	%	Country	%
Switzerland	26.1	United Kingdom	20.7
Ireland	20.7	Germany	17.2
Belgium	17.2	Finland	16.6
Czech Republic	16.3	Denmark	16
Hungary	15.5	Spain	12.4
Portugal	11.6	France	11
Norway	10.4	Netherlands	10.0
Austria	8.9	Italy	7.9
Sweden	7.8		

Source: AESGP/IMSSelf-Medication.

to assume that future drug switches will provide better OTC products than what are currently available.

a. "Domino Effect" Theory of Indications

Of course, there are still issues regarding the OTC treatment of chronic or recurring illness. Monitoring and compliance questions remain mostly unanswered at this time. However, once some of the conceptual issues are addressed satisfactorily, there will be a kind of domino effect on several indications, such as cholesterol, osteoporosis, and hypertension.

We see a significant opening up of acceptable OTC treatments in the near future. Add to this some recent history on the ever-present issue of cost containment, and you have a more complete story. Discipline is being imposed on the Rx business on a global basis. National health care debt is a serious issue for most governments. If managed properly, the OTC industry will benefit and grow stronger.

For example, a country like France is in extraordinary trouble. France's estimated 1997 national health care debt was US $49 billion. It has the highest per capita expenditure ($235) on Rx drugs in the world. The United States ranks third. Virtually all major countries have identified this problem. Many are experimenting with a kind of "managed care." Reform of health care is proving difficult, but it can be accomplished. The United Kingdom has been the most successful so far. Their Medicines Control Agency (MCA) is very successful from a health care standpoint. The MCA returned money to the government, because it came in under budget last year.

Table 6 Experiments in Managed Care: US, UK, Germany, and France—Constraints on Growth of Prescription Costs

Country	General Practitioners as Gatekeeper	Ceiling on MD Rx budgets	$ Penalties for MDs	Pharma Co. Taxes
US	Yes	No	No	No
UK	Yes	No	No	No
Germany	Yes	Yes	Yes	Yes
France	Yes	Yes	Yes	Yes

Source: SWITCH Newsletter.

Table 6 is an example of the kinds of discipline the Rx business is experiencing.

The (GP) has become the universal gatekeeper. Specialists are dependent on the GP for referrals. In the last year, financial penalties were possible if doctors prescribed more than their approved budget levels in some countries.

Why is it so hard to imagine a doctor prescribing reimbursable OTCs? In the United Kingdom and Germany, it is common. In the United States, a recent survey stated that HMOs reimbursed 41% of OTC antihistamines and 36% of H_2 antagonists. The survey predicted that the number of products and the rate of reimbursement will increase during the next 2 years.

The HMOs are beginning to understand that drugs are a much safer and cheaper alternative to surgery. For example, a vagotomy, which is a surgical removal of a peptic ulcer, is now unnecessary thanks to H_2-receptor antagonists. It is estimated that in the United States, this has saved more than $3 billion a year.

According to the recent trends, the Rx-to-OTC future appears challenging but bright.

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Industry and FDA Liaison

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I. INTRODUCTION

One of the most important groups in a pharmaceutical company is the department of Drug Regulatory Affairs (DRA). Its personnel are largely responsible for establishing a liaison with their counterparts at the U.S. FDA. This chapter will describe the activities of the FDA, emphasizing the center responsible for the review and approval of INDs and NDAs, namely the CDER.

The FDA is an agency within the PHS, which in turn is a part of the DHHS. The FDA regulates over $1 trillion worth of products, which account for 25 cents of every dollar spent annually by American consumers. The FDA touches the lives of virtually every American, every day, for it is FDA's job to see that the food we eat is safe and wholesome, the cosmetics we use will not harm us, the medicines and medical devices we use are safe and effective, and radiation-emitting products such as microwave ovens will not cause harm. Feed and drugs for pets and farm animals also come under FDA scrutiny. The FDA also ensures that all of these products are labeled truthfully with the information people need to use them properly.

The FDA is one of our nation's oldest consumer protection agencies. Its approximately 9,000 employees monitor the manufacture, import, transport, storage, and sale of about $1 trillion worth of products each year. It does so at a cost to the taxpayer of about $3 per person. First and foremost, FDA is a public health agency, charged with protecting American consumers by enforcing the Federal Food, Drug, and Cosmetic Act and several related public health laws. To carry out this mandate of consumer protection, FDA has some 1,100 investigators and inspectors who cover the country's almost 95,000 FDA-regulated businesses. These employees are located in district and local offices in 157 cities across the country.

A. Inspections and Legal Sanctions

These investigators and inspectors visit more than 15,000 facilities a year, seeing that products are made correctly and labeled truthfully. As part of their inspections, they collect about 80,000 domestic and imported product samples for examination by FDA scientists or for label checks. If a company is found violating any of the laws that FDA enforces, FDA can encourage the firm to correct the problem voluntarily or to recall a faulty product from the market. A recall is generally the fastest and most effective way to protect the public from an unsafe product.

When a company cannot or will not voluntarily correct a public health problem with one of its products, FDA has legal sanctions it can bring to bear. The agency can go to court to force a company to stop selling a product and to have items already produced seized and destroyed. When warranted, criminal penalties, including prison sentences, are sought against manufacturers and distributors.

About 3,000 products a year are found to be unfit for consumers and are withdrawn from the marketplace, either by voluntary recall or by court-ordered seizure. In addition, about 30,000 import shipments a year are detained at the port of entry because the goods appear to be unacceptable.

B. Scientific Expertise

The scientific evidence needed to back up FDA's legal cases is prepared by the agency's 2,100 scientists, including 900 chemists and 300 microbiologists, who work in 40 laboratories in the Washington, D.C., area and around the country. Some of these scientists analyze samples to see, for example, if products are contaminated with illegal substances. Other scientists review test results submitted by companies seeking agency approval for drugs, vaccines, food additives, coloring agents, and medical devices. The FDA operates the National Center for Toxicological Research at Jefferson, Arkansas, which investigates the biological effects of widely used chemicals. The agency also runs the Engineering and Analytical Center at Winchester, Massachusetts, which tests medical devices, radiation-emitting products, and radioactive drugs.

Assessing risks—and, for drugs and medical devices, weighing risks against benefits—is at the core of FDA's public health protection duties. By ensuring that products and producers meet certain standards, FDA protects consumers and enables them to know what they are buying. For example, the agency requires that drugs—both prescription and over-the-counter—be proven safe and effective. The agency must determine that the new drug produces the benefits it is supposed to without causing side effects that would outweigh those benefits.

C. Product Safety

Another major FDA mission is to protect the safety and wholesomeness of food. The agency's scientists test samples to see if any substances, such as pesticide residues, are present in unacceptable amounts. If contaminants are identified, FDA takes corrective action. They also set labeling standards to help consumers know what is in the foods they buy. The nation's food supply is protected in yet another way, as FDA sees that medicated feeds and other drugs given to animals raised for food are not threatening to the consumer's health.

The safety of the nation's blood supply is another FDA responsibility. The agency's investigators routinely examine blood bank operations, from record-keeping to testing for contaminants. The FDA also ensures the purity and effectiveness of agents such as insulin and vaccines.

Medical devices are classified and regulated according to their degree of risk to the public. Devices that are life-supporting, life-sustaining, or implanted, such as pacemakers, must receive agency approval before they can be marketed.

The FDA's scrutiny does not end when a drug or device is approved for marketing; the agency collects and analyzes tens of thousands of reports each year on drugs and devices after they have been put on the market to monitor for any unexpected adverse reactions.

Cosmetic safety also comes under FDA's jurisdiction. The agency can have unsafe cosmetics removed from the market. The dyes and other additives used in drugs, foods, and cosmetics are subject to FDA scrutiny. The agency must review and approve these chemicals before they can be used.

The FDA is headed by Commissioner Jane E. Henney, M.D. Dr. Henney was appointed FDA Commissioner in November 1998 after a 2-year period during which FDA did not have a commissioner. Prior to her position with FDA, Dr. Henney served as the first Vice President of the University of New Mexico Health Sciences Center from 1994 to 1998. Before joining UNM, she served as the Deputy Commissioner for Operations at the FDA from 1992 to 1994. Her other past academic administrative positions have included Vice Chancellor for Health Programs and Policy at the University of Kansas and Acting Director of the University of Kansas Mid America Cancer Center from 1985 to 1992. She also served as Interim Dean of the School of Medicine at the University of Kansas from 1987 to 1989. From 1976 to 1985, Dr. Henney held various positions at the NCI. From 1980 to 1985, she was the Deputy Director of the NCI.

II. THE CENTER FOR DRUG EVALUATION AND RESEARCH ORGANIZATION

Understanding how CDER is organized is important in the strategic planning of how best to interact with the various divisions and offices responsible for new drug approval process. As of January 1999, there are 15 review divisions within CDER (including the Division of Over-the-Counter drug products) that are responsible for reviewing all INDs, NDAs, and chemistry and efficacy supplemental applications. Deciding which division will be assigned to a particular IND or NDA depends solely on the indication for the new drug. Divisions are organized on the basis of therapeutic uses for new products, and the divisions are staffed with experts in a particular pharmacotherapeutic area. The current divisions include: Cardiorenal; Neuropharmacological; Oncology; Pulmonary; Metabolic and Endocrine; Reproductive and Urologic; Gastrointestinal and Coagulation; Anesthetic, Critical Care, and Addiction; Medical Imaging and Radiopharmaceutical; Antiviral; Antiinfective; Special Pathogen and Immunologic; Anti-Inflammatory, Analgesic and Ophthalmologic; and Dermatologic and Dental Drug Products.

The 15 divisions are grouped among one of five ODEs. The ODE I, for example, has administrative control for the divisions of Cardiorenal, Neuropharmacological, and Oncologic Drug Products. The DDMAC also is a part of this Office. The organizational chart for CDER and its component parts is usually updated quarterly, and these updates may be found on the internet at: http://www.fda.gov/cder/cderorg.htm. The Center for Drug Evaluation and Research is organized into three main offices: the OCD, the ORM, and the OPS.

The OCD encompasses the executive operations staff, regulatory policy staff, the ombudsman, and the equal employment opportunity and diversity management staff. The executive operations staff provides support to the OCD, including coordinating executive and legislative activities; managing the preparation and coordination of center-level meetings; and responding to written correspondence from constituents. The regulatory policy staff initiates, develops, and reviews regulations, policies, procedures, and guidances that affect the drug review process. This includes creating and publishing CDER's Manual of Policies and Procedures, preparing *Federal Register* notices for publications, and responding to citizen petitions. The primary mission of the ombudsman is to receive complaints, investigate and act on them, mediate disputes, and, in general, attend to problems involving interpersonal working relationships.

The ORM develops and implements drug review management and scientific policies, including prescription drug user-fee policies. With support from the OPS on chemistry and manufacturing controls and biopharmaceutical issues, this office reviews all INDs and NDAs for human drugs, except generic drug applications. In addition, ORM evaluates for safety and effectiveness NDAs for

OTC drug products and handles prescription drug switches to OTC drug status. It develops and implements safety and effectiveness standards for prescription and OTC drug products and provides direction and policy formulation for pharmacology and toxicology issues.

The OPS provides scientific and regulatory support in several areas. It develops and implements review management and scientific policies pertaining to the generic drug review process. It also is the office providing the management and scientific policies pertaining to the new drug review process for chemistry, manufacturing, and controls; clinical pharmacology; and biopharmaceutics for both INDs and NDAs. Other OPS activities include developing and implementing policies and directing programs through applied regulatory research; developing and implementing standards for generic drugs and new drugs that enhance the drug development and regulatory review processes; and providing scientific oversight of CMC and sterility sections of INDs, NDAs, and supplements. The office also oversees microbiology, biopharmaceutics, and clinical pharmacology aspects of regulatory submissions.

All drugs, upon FDA receipt of an IND filing, are classified on the basis of their anticipated indication(s) for use and assigned to one of the 15 divisions. In addition to the director in charge, each division has personnel with responsibilities in scientific review areas. For each IND or NDA, a "drug review team" is established to provide the appropriate expertise to allow for a judgment regarding the drug's overall acceptance based on its safety, clinical efficacy, and manufacturing information, provided to the FDA by the sponsor of the drug application.

The CDER drug review team members apply their individual, special technical expertise to review INDs or new drug applications.

Each review division employs a team of *chemists* responsible for reviewing the chemistry and manufacturing and controls sections of drug applications. In general terms, chemistry reviewers address issues related to drug identity, manufacturing control, and analysis. The reviewing chemist evaluates the manufacturing and processing procedures for a drug to ensure that the compound is adequately reproducible and stable. If the drug is either unstable or not reproducible, then the validity of any clinical testing would be undermined, because one would not know what was really being used in patients, and, more importantly, studies could pose significant risks to participants.

At the beginning of the chemistry and manufacturing section, the drug sponsor should state whether it believes the chemistry of either the drug substance or the drug product—or the manufacturing of either the drug substance or the drug product—present any potential human risk. If so, these risks should be discussed, with steps proposed to monitor them.

In addition, sponsors should describe any chemistry and manufacturing differences between the drug product proposed for clinical use and that used in the animal toxicology trials that formed the basis for the sponsor's conclusion that it was safe to proceed with the proposed clinical study. How these differences might affect the safety profile of the drug product should be discussed. If there are no differences in the products, that should be stated.

The *pharmacology/toxicology* review team is staffed by pharmacologists and toxicologists who evaluate the results of animal testing and attempt to relate animal drug effects to potential effects in humans. In the area of pharmacology and drug disposition, an application should generally contain: (a) a description of the pharmacologic effects and mechanism(s) of action of the drug in animals, and (b) information on the absorption, distribution, metabolism, and excretion of the drug. For toxicology studies, the types of studies needed depend on the nature of the drug but will typically include short- and long-term studies, including the potential for drugs to induce birth defects or cancer in humans.

Medical/clinical reviewers, often called medical officers, are almost exclusively physicians. In rare instances, nonphysicians are used as medical officers to evaluate drug data. Medical reviewers are responsible for evaluating the clinical sections of submissions, such as the safety of the clinical protocols in an IND or the results of this testing as submitted in the NDA. Within most divisions, clinical reviewers take the lead role in the IND or NDA review and are responsible for synthesizing the results of the animal toxicology, human pharmacology, and clinical reviews to formulate the overall basis for a recommended agency action on the application.

During the IND review process, the medical reviewer evaluates the clinical trial protocol to determine: (a) if the participants will be protected from unnecessary risks, and (b) if the study design will provide data relevant to the safety and effectiveness of the drug. Under federal regulations, proposed phase 1 studies are evaluated almost exclusively for safety reasons. Since the late 1980s, FDA reviewers have been instructed to provide drug sponsors with greater freedom during phase 1, as long as the investigations do not expose participants to undue risks. In evaluating phase 2 and 3 investigations, however, FDA reviewers also must ensure that these studies are of sufficient scientific quality to be capable of yielding data that can support marketing approval.

Other reviewers include *statisticians*, *microbiologists*, and *biopharmaceutical experts*. Statisticians evaluate the statistical relevance of the data in the NDA, with the main tasks being to evaluate the methods used to conduct studies and those used to analyze the data. The purpose of these evaluations is to give the medical officers a better idea of the power of the findings to be extrapolated to the larger patient population in the country.

Clinical microbiology information is required only in NDAs for anti-infective drugs. Because these drugs affect microbial, rather than human physiology, reports on the drugs' in vivo and in vitro effects on the target microorganisms are critical for establishing product effectiveness.

An NDA's microbiology section usually includes data describing:

The biochemical basis of the drug's action on microbial physiology
The drug's antimicrobial spectra, including results of in vitro preclinical studies demonstrating concentrations of the drug required for effective use
Any known mechanisms of resistance to the drug, including results of any known epidemiologic studies demonstrating prevalence of resistance factors
Clinical microbiology laboratory methods needed to evaluate the effective use of the drug.

Pharmacokineticists/biopharmaceuticists evaluate the rate and extent to which the drug's active ingredient is made available to the body and the way it is distributed in, metabolized by, and eliminated from the human body.

All team members work together to assure that the label and the labeling are accurate and provide clear instructions to health care practitioners or to consumers of OTC products.

A key member of the review team is the project manager, formerly called the consumer safety officer or CSO. The project manager evaluates regulatory information to determine compliance with current policies and regulations. In addition, project managers orchestrate and coordinate the drug review team(s) interactions, efforts, and reviews and they serve as the CDER review team's primary contact with the drug industry. They may be considered as the liaison between the FDA and industry.

The total full-time equivalent staff working in CDER is just under 2000. The number of FDA staff has increased in recent years as a result of the PDUFA of 1992 and the renewal of PDUFA in the FDA Modernization Act of 1997. On average, each of the five ODEs have about 125–135 employees. Because there are essentially three divisions per office, the average staff in a particular division is about 40–45, including clerical, secretarial, and project management support. Updates of these organizational charts may be found on the internet at http://www.fda.gov/cder/cderorg.htm.

III. CONTACTS WITH FDA

One of CDER's primary goals is to work collaboratively and cooperatively with industry, academia, and others to improve the drug development and review process. It also strives to provide consumers and health care providers with drug information that is vital to improving the public health. The topics listed below provide an overview of the various means of communicating with CDER.

A. Consumer/Industry Inquiries

The FDA's CDER is dedicated to ensuring that all persons involved in, or who depend upon, drug regulation excellence have the information needed to develop, review, market, dispense, prescribe, or use drugs safely and effectively.

To enhance the communications aspect of this process, the Center created the OTCOM's Division of Communications Management (DCM). This division enhances information exchange, strategic communications planning, and the development of communications products and initiatives. The Division of Communications Management works to ensure that pharmaceutical industry representatives, health care professionals, government officials, and consumers have easy and open access to information and are educated about the drug regulation process and the benefits and risks of drugs.

Any of these individuals or groups may request information on specific drugs, guidance documents, publications, or general information such as a description of the drug approval process.

There are a number of ways consumers and industry representatives can communicate with or get reliable, current, and up-to-date information from the Center.

1. The newest, easiest method for getting information is the Center's world wide web homepage at http://www.fad.gov/cder.
2. Another easy method is the Center's fax-on-demand system, which contains literally hundreds of documents for consumers, industry, federal, state, and local agencies, and foreign government representatives. The number is 1-800-342-2722.
3. For more specific or complex drug inquiries, individuals may telephone the Drug Information Branch at (301) 827-4573 or send an electronic mail message at dib@cder.fda.gov.
4. For specific inquiries from industry, CDER's Compendia Operations can be called at (301) 594-0104.

Other sources of information include:

1. The FDA Office of Consumer Affairs at 1-800-532-4440, or locally at (301) 827-4420
2. The FDA's OPA at (301) 443-1130

In addition, consumers and industry representatives can contact:

1. CDER ombudsman, Jim Morrison, (301) 594-5443
2. FDA Freedom of Information Staff, (301) 827-6567
3. FDA MedWatch Office, 1-800-FDA-1088

B. Industry/FDA Inquiries

All meetings with the FDA are held at the pleasure of the agency and should be requested judiciously. Project managers (CSOs), a large percentage of whom were former FDA field investigators, are responsible for coordinating FDA/industry meetings. Their other duties include acting as the contact point between the division and the regulated industry; preparing minutes of FDA/industry meetings; and assisting the division with the FDA advisory committee meetings.

If a meeting with the FDA is deemed necessary, the first step is to telephone the project manager assigned to the firm's IND or NDA. The need for a meeting should be explained, a statement about the general topic of the meeting should be described, and an idea of when the meeting is needed should be offered. The project manager will likely return the call and indicate if a meeting will be granted. If the answer is positive, a confirmatory letter from the firm should be sent to the appropriate division. The document should include the fact that the meeting has been granted and what the date for the meeting will be. The names and titles of those representatives of the sponsor who will be attending the meeting and the proposed agenda with the topics to be discussed spelled out in some detail is provided. Typically it will be 4, and more likely 6 weeks after the initial telephone contact with FDA before the meeting will be held. If the meeting requires FDA review of material, as a large percentage of meetings do, the premeeting document should be submitted with the letter. If the information to be discussed is already on file with FDA, the letter should detail by submission number what documents in an IND or NDA should be referred to. It is always appropriate to contact the project manager within the division by telephone to reconfirm the meeting about 2 weeks before the established meeting date. In February 1999, CDER issued a draft guidance document entitled: Formal Meetings With Sponsors and Applicants for PDUFA Products. It may be found on the Internet at: http://www.fda.gov/cder/guidance/2125dft.pdf.

C. Pre-IND/Preclinical Meetings

Prior to clinical studies, the sponsor needs to demonstrate evidence that the compound is biologically active, and both the sponsor and the FDA need data showing that the drug is reasonably safe for initial administration to humans; hence the filing of an IND. Preclinical meetings are occasionally conducted with the appropriate division that would review the IND or the drug marketing application, and these meetings are typically requested by the sponsor of a drug. Meetings at such an early stage in the process are sometimes useful opportunities for open discussion about testing phases, data requirements, and any scientific issues that may need to be resolved prior to IND submission. At these meetings, the sponsor and the FDA discuss and agree upon the design of the animal studies needed to initiate human testing, and perhaps may discuss the types of clinical testing that would best demonstrate the safety and efficacy of the drug in humans.

It is sometimes difficult to know when it is necessary or prudent to request a pre-IND conference with the FDA prior to the filing of an IND. This decision frequently depends on the history of the new compound. If one is dealing with a new chemical entity that has been synthesized in the United States and on which minimal preclinical and clinical investigations have been conducted, there is seldom a need to review data with the FDA prior to submitting the IND. There are, however, exceptions to this statement. They reflect the nature of the proposed indication, the use of new technology (e.g., recombinant DNA techniques), the expected human toxicity based on animal data, the design of the initial clinical trials, or appropriate efficacy criteria to be monitored.

On the other hand, an IND may be submitted for a compound that has been developed overseas and may even be marketed in one or more offshore countries. In this case, the data comprising the IND will be more voluminous. Many preclinical reports will need to be evaluated and summarized, and a large number of clinical reports and perhaps a significant amount of published literature may need to be reviewed, summarized, and presented to regulatory personnel. It is also possible that the sponsor has accumulated sufficient data on the compound from these sources to support both calculations regarding its safety and initiation of an IND with a phase 2 clinical investigation. Any or all of the above circumstances point to a discussion with appropriate division staff prior to IND filing—a staff that may help the FDA as well as the drug's sponsor. In the course of such a meeting, some agreement should be reached on a phase of clinical investigation that will be acceptable to the FDA for the initial study protocols to be included in the original IND submission. The FDA will then be alerted to the filing and can plan to review the IND armed with the prior information received during the meeting.

In preparing for a pre-IND meeting, the DRA representative should provide the FDA with summary documents of the subjects to be discussed. The question of confidentiality must be carefully considered. With no IND filing reference number, the information submitted should be general in nature. Complete details of the synthesis and chemical structure should not be provided. It is usually sufficient to vaguely describe the compound and identify it by code number.

The only division in CDER with an established policy regarding pre-IND consultation meetings is the Division of Anti-Viral Drug Products (DAVDP). Established in 1988, the DAVDP pre-IND Consultation Program is a proactive strategy designed to facilitate informal early communications between DAVDP and potential sponsors of new therapeutics for the treatment of AIDS and life-threatening opportunistic infections, other viral infections, and soft tissue transplantation. Pre-IND advice may be requested for issues related to drug development plans; data needed to support the rationale for testing a drug in humans; the design of nonclinical pharmacology, toxicology, and drug activity studies; data requirements for an IND application; and regulatory requirements for demonstrating safety and efficacy. All potential drug sponsors/developers working in the antiviral area are encouraged to initiate contact with the division as early in the drug development process as possible so that they will have the opportunity to consider the recommendations of DAVDP in planning their preclinical and clinical development programs. The individual to contact is the Pre-IND project manager within the DDAVP.

D. End-of-Phase 2 Conference

The primary focus of "end-of-phase 2" meetings is to determine whether it is safe to begin phase 3 testing. This is also the time to plan protocols for phase 3 human studies and to discuss and identify any additional information that may be required to support the submission of an NDA. It is also intended to establish an agreement between the agency and the sponsor of the overall plan for phase 3 and the objectives and design of particular studies. These meetings avoid unnecessary expenditures of time and money because data requirements have been clarified.

One month before the end-of-phase 2 meeting, the sponsor should submit the background information and summary protocols for phase 3 studies. This information should include data supporting the claim of the new drug product, chemistry data, animal data and proposed additional animal data, results of phase 1 and 2 studies, statistical methods being used, specific protocols for phase 3 studies, as well as a copy of the proposed labeling for the drug, if available. This summary provides the review team with information needed to prepare for a productive meeting.

In the past, only selected NDA candidate drug sponsors were encouraged to request an End-of-Phase 2 conference. Today, all holders of an IND for new chemical entities are entitled to this important conference. Depending on the workload of the division responsible for review of the IND, however, requests for a meeting for an end-of-phase 2 conference may be easier to arrange if the conference requested is for one of the following:

1. New molecular entities for a high priority review drug
2. Drugs with important toxicity problems
3. A compound representing a moderate therapeutic gain but not assigned as a high priority drug
4. A marketed drug with an important new indication under study

IV. PREPARING FOR AN END-OF-PHASE 2 CONFERENCE

There are a number of checkpoints worth observing in preparing for the end-of-phase 2 conference. Key elements are listed below.

1. Ascertain that there have not been pauses in clinical studies between phase 1 and phase 2. The FDA's policies regarding no pauses apply to the usual situation in which research on a drug progresses without serious adverse incidents. This statement does not, however, take precedence over the FDA's responsibility, when necessary, to stop or limit clinical trials for reasons of safety. (Summary phase 1 data along with the necessary chronic toxicity reports should be submitted to support the safety of phase 2 studies when they are initiated.)

2. There also should be no pause between phases 2 and 3 clinical studies. For maximum benefit, the end-of-phase 2 conference should be timed as close as possible to the start of multiple phase 3 studies.

3. There is no clearcut dividing line between phase 2 and 3. (The latter usually includes well-controlled clinical trials of the type performed during phase 2, but in larger populations, under less-controlled conditions.) The sponsor of an IND should carefully determine the time when late phase 2 has been clearly passed (efficacy has been essentially demonstrated statistically to a sufficient degree of confidence) and the drug is ready for phase 3 development. At this point, with phase 3 plans defined, a meeting with FDA is appropriate.

4. To aid in the review of phase 2 data, the sponsor must prepare a summary separately presenting the results and conclusions for each investigation or multi-investigator study; conclusions should be supported by appropriate statistical analyses. When results from more than one institution or investigator are presented under a single protocol, the information should be summarized so that data from each investigator or institution can be readily identified.

5. Be prepared to provide the following items for the end-of-phase 2 conference, representing each protocol under which the clinical studies have been performed:

    a. Tables showing the number of patients (a) randomly assigned for each treatment category according to the protocol, (b) actually entered into each treatment category, (c) lost or prematurely withdrawn from the study, and (d) summarized by pertinent selection criteria.
    b. A list explaining why patients were lost or prematurely withdrawn from the study and the number of subjects lost or withdrawn for each investigator. The number of days that each of the patients spent in the study also should be submitted.
    c. A summary of the pertinent procedures used to obtain baseline infor-

mation, measurements of effectiveness, and safety tests performed according to each applicable test or measure. Also prepare a table showing the frequency of testing, the unit of measurement, and the number of patients actually checked as of the reported date. Be sure to include normal values for each investigator's laboratory.

d. For each investigator, summarize baseline and final results of the study in terms of the appropriate variables used to measure safety and effectiveness of the drug under investigation.
e. A statement describing whether statistical analysis has been applied in evaluating the data, and justification of the adequacy of such analysis.
f. If requested, submit the "hard copy" of raw data used in the construction of the summary report. Clinical records or case report forms should be organized and identified for convenient reference and review. If large amounts of data are involved, automatic, processible formats such as easily accessible computer files on disk or computer tape may also be requested by the FDA.

The end-of-phase 2 conference should examine and appraise the adequacy of the phase 2 studies with respect to answering essential questions about the safety and effectiveness in humans for the claimed indications, the safety of proceeding to phase 3, the suitability of the phase 3 protocols, the completeness of the animal toxicity and pharmacology studies, and the manufacturing and controls data.

To address these and related matters, appropriate personnel from the company and the FDA should be present. The FDA will have medical reviewers and a statistician attend all meetings. Whether a pharmacologist, chemist, or microbiologist need attend these sessions will depend on the circumstances. An FDA consultant may be invited, or a review of the consultant's data may be presented in his or her absence. The sponsor also may bring to the meeting one or more consultants. Minutes of the conference will be prepared by the FDA, and allowances are made for the sponsor to prepare and submit minutes to the file.

Finally, the draft meeting guidance discussed in Section III.B should be reviewed.

A. End-of-Phase 2 Conference—Summary

When a firm has reached the end of phase 2, it should contact the appropriate division at the FDA to arrange for a conference. All clinical data should be summarized, tabulated, and statistically analyzed, as described. These data, together with any additional preclinical and manufacturing and controls data, and plans and protocols for phase 3 should be submitted at least 1 month in advance of the scheduled meeting. A copy containing only clinical data, as a rule, plus the proposed protocols for phase 3, should be provided for the FDA statistician. The submission also should include any specific questions the firm wishes to discuss.

Discussions should be limited to those indications of the drug that the sponsor intends to claim. Agreements should be reached at the conference on the adequacy of, or deficiencies in, the submitted data, or the proposed protocols for phase 3 studies. Specific proposals for correcting deficiencies, for performing additional studies, or not performing what might be considered an excess of studies, should be reviewed and agreed to. The minutes of the conference and the follow-up letter from the firm will serve as a permanent record of these agreements. Barring new and significant scientific developments, a major improvement in the state of the art, unforeseen circumstances occurring during further investigation of the drug, or major inaccuracies in the summarized data noted after full review of the NDA, these agreements shall have the same status as advisory opinions in that they are binding on the FDA. The execution of the agreed upon studies, nevertheless, does not guarantee approval of the subsequent NDA. Any NDAs submitted after end-of-phase 2 conferences that are deficient in satisfying the recorded or subsequently modified agreements still may require additional studies to be considered approvable. Food and Drug Administration commitments will not necessarily be considered binding if the sponsor fails to comply with agreed-upon commitments.

V. PRE-NDA MEETINGS

The purpose of a pre-NDA meeting is to discuss the presentation of data (both paper and electronic) in support of the application. The information provided at the meeting by the sponsor includes:

A summary of clinical studies to be submitted in the NDA
The proposed format for organizing the submission, including methods for presenting the data
Other information that needs to be discussed

The meeting is conducted to uncover any major unresolved problems or issues; to identify studies the sponsor is relying on as adequate and well controlled in establishing the effectiveness of the drug; to help the reviewers to become acquainted with the general information to be submitted; and to discuss the presentation of the data in the NDA to facilitate its review. Once the NDA is filed, a meeting may also occur 90 days after the initial submission of the application to discuss issues that are uncovered in the initial review.

VI. ADVISORY COMMITTEE MEETINGS

All of the FDA's current advisory committees are scientific and technical committees. Advisory committees have been established to advise and make recommendations on issues related to the agency's regulatory responsibilities. The primary role of FDA advisory committees is to provide independent expert scientific advice to the agency in its evaluation of regulated products, and to help make sound decisions based on the reasonable application of good science. The committees are advisory in nature, and final decisions are made by the FDA. They consist of individuals with recognized expertise and judgment in a specific field who have the training and experience necessary to evaluate information objectively and to interpret its significance under various, often controversial, circumstances. Advisory committees weigh available evidence and provide scientific and medical advice on the safety, effectiveness, and appropriate use of products under FDA jurisdiction. Another role is to advise the agency on general criteria for evaluation and on broad regulatory and scientific issues that are not related to a specific product. Although advisory committees have a prominent role in the product approval stage, they are sometimes used earlier in the product development cycle and may be invited to consider postmarketing issues.

The charter of each of the advisory committees provides for at least one member to represent the consumer perspective. Consumer representatives make a valuable contribution by raising concerns that might not be otherwise addressed before products come to the marketplace. As they participate in the advisory committee process, consumer members become more knowledgeable about FDA issues and products that are often on the cutting edge of new research and technology. They gain the experience of working with nationally recognized scientific experts.

The current CDER advisory committees include the following:

Anesthetic and Life Support Drugs Advisory Committee
Anti-Infective Drugs Advisory Committee
Antiviral Drugs Advisory Committee
Arthritis Advisory Committee
Cardiovascular and Renal Drugs Advisory Committee
Dermatologic Drugs Advisory Committee
Drug Abuse Advisory Committee
Endocrinology and Metabolic Drugs Advisory Committee
Gastrointestinal Drugs Advisory Committee
Medical Imaging Drugs Advisory Committee
Nonprescription Drugs Advisory Committee
Oncologic Drugs Advisory Committee
Peripheral and Central Nervous System Drugs Advisory Committee

Pharmaceutical Science Drugs Advisory Committee
Psychopharmacologic Drugs Advisory Committee
Pulmonary Allergy Drugs Advisory Committee
Reproductive Health Drugs Advisory Committee

At times, CDER may especially want a committee's opinion about a new drug, a major indication for an already approved drug, or a special regulatory requirement being considered, such as a boxed warning in a drug's labeling. Committees may also advise CDER on necessary labeling information or help with guidelines for developing particular kinds of drugs. They may also consider questions such as whether a proposed study for an experimental drug should be conducted or whether the safety and effectiveness information submitted for a new drug is adequate for marketing approval.

In October 1998, FDA published a guidance for industry entitled *Advisory Committees: Implementing Section 120 of the Food and Drug Administration Modernization Act of 1997.* This document provided guidance for industry on changes to the policies and procedures being used by CDER regarding advisory committees in response to section 120 of the FDA Modernization Act of 1997 (FDAMA). This section of the FDAMA directed FDA to establish panels of experts, or to use already-established panels of experts, to provide scientific advice and recommendations to the agency regarding the clinical investigation of drugs or the approval for marketing of drugs. The FDA has defined the term "panel of experts" to mean "advisory committees."

Section 120 of FDAMA amended section 505 of the FD&C Act by adding section 505(n). This new section includes provision for the following: (a) additional members to be included in new advisory committees, (b) new conflict of interest considerations, (c) education and training for new committee members, (d) timely committee consideration of matters, and (e) timely agency notification to affected persons of decisions on matters considered by advisory committees.

VII. FDA INITIATIVES TO SPEED DRUG APPROVAL

The FDA has instituted several programs designed to hasten the drug approval process for effective drugs. Pharmaceutical regulatory professionals should be aware of any and all ways that can be recommended to their research and management staff for more rapid drug approval. These FDA alternatives to expeditious new drug approval are described below.

Subpart E in Section 312 of the Code of Federal Regulations establishes procedures to expedite the development, evaluation, and marketing of new therapies intended to treat people with life-threatening and severely debilitating illnesses, especially where no satisfactory alternatives exist.

A. Accelerated Development/Review Program

The first is the accelerated development/review program. Accelerated development/review (see Federal Register, April 15, 1992) is a highly specialized mechanism for speeding the development of drugs that promise significant benefit over existing therapy for serious or life-threatening illnesses. This process incorporates several novel elements aimed at making sure that rapid development and review are balanced by safeguards to protect both the patient and the integrity of the regulatory process.

Accelerated development/review can be used under two special circumstances: (a) when approval is based on evidence of the product's effect on a "surrogate end point," and (b) when the FDA determines that safe use of a product depends on restricting its distribution or use. A surrogate end point is a laboratory finding or physical sign that may not be a direct measurement of how a patient feels, functions, or survives but is still considered likely to predict therapeutic benefit for the patient.

The fundamental element of this process is that the manufacturers must continue testing after approval to demonstrate that the drug indeed provides therapeutic benefit to the patient. If not, the FDA can withdraw the product from the market more easily than usual.

B. Treatment IND

Treatment INDs (see Federal Register, May 22, 1987) are used to make promising new drugs available to desperately ill patients as early in the drug development process as possible. The FDA will permit an investigational drug to be used under a treatment IND if there is preliminary evidence of drug efficacy and the drug is intended to treat a serious or life-threatening disease, or if there is no comparable alternative drug or therapy available to treat that stage of the disease in the intended patient population. In addition, these patients are not eligible to be in the definitive clinical trials, which must be well under way, if not almost finished.

An immediately life-threatening disease means a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months, or in which premature death is likely without early treatment. For example, advanced cases of AIDS, herpes simplex encephalitis, and subarachnoid hemorrhage are all considered immediately life-threatening diseases. Treatment INDs are made available to patients before general marketing begins, typically during phase 3 studies. Treatment INDs also allow FDA to obtain additional data on the drug's safety and effectiveness.

C. FDA Guidance Documents/Guidelines

A regulatory professional must be aware of the guidance documents that FDA has made available to assist industry to understand expectations regarding drug development and the approval process. The website providing the complete list of FDA guidances is updated almost daily. It may be accessed at http://www.fda.gov/cder/guidance/index.htm.

The FDA comprehensive list of all guidances available is found on the internet at http://www.fda.gov/cder/guidance/guidlist.pdf.

The FDA guidance page is subdivided into the following sections for ease of use: advertising; biopharmaceutics (final and draft); chemistry (final and draft); clinical/antimicrobial (draft); clinical/medical (final and draft); compliance (final and draft); generics (final and draft); industry letters; information technology; international congress on harmonization (final and draft); IND; labeling; microbiology; modernization act; OTC; pharm/tox; and procedural.

VIII. FREEDOM OF INFORMATION

Freedom of information is another important way in which regulatory personnel may readily obtain information from the FDA. The FDA has a guidance handbook published intended to facilitate requests for both public information and records not originally prepared for distribution by the FDA. This handbook has been updated in response to the Electronic Freedom of Information Act (FOIA) amendments of 1996.

A. Obtaining Public Information

Certain documents that are prepared for public distribution—press releases, consumer publications, speeches, and congressional testimony—are available from the FDA without having to file an FOIA request. Many of these documents are available on FDA's internet site (http://www.fda.gov/). Consumers with questions about FDA-related matters also may write to the Office of Consumer Affairs, HFE-88, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, or call toll free, 1-888-FDA-INFO (1-888-322-4636).

B. Obtaining Information Through FOIA

The Freedom of Information Act allows anyone to request copies of records not normally prepared for public distribution. It pertains to existing records only and does not require agencies to create new records to comply with a request. It also does not require agencies to collect information they do not have or to do research or analyze data for a requestor. In addition, FOIA requests must be specific enough to permit an FDA employee who is familiar with the subject matter to locate records in a reasonable period.

Under FOIA, certain records may be withheld in whole or in part from the requestor if they fall within one of nine FOIA exemptions. Six of these exemptions most often form the basis for the withholding of information by the FDA:

Exemption 2 protects certain records related solely to the FDA's internal rules and practices.

Exemption 3 protects information that is prohibited from disclosure by other laws.

Exemption 4 protects trade secrets and confidential commercial or financial information.

Exemption 5 protects certain interagency and intra-agency communications.

Exemption 6 protects information about individuals in personnel, medical, and similar files when disclosure would constitute a clearly unwarranted invasion of privacy.

Exemption 7 protects records or information compiled for law enforcement purposes when disclosure (a) could reasonably be expected to interfere with enforcement proceedings, (b) would deprive a person of a right to a fair trial or an impartial adjudication, (c) could reasonably be expected to constitute an unwarranted invasion of personal privacy, (d) could reasonably be expected to disclose the identity of a confidential source, (e) would disclose techniques and procedures for law enforcement investigations or prosecutions, or would disclose guidelines for law enforcement investigations or prosecutions, if such disclosure could reasonably be expected to risk circumvention of the law, or (f) could reasonably be expected to endanger the life or physical safety of an individual.

In the event the FDA relies on one or more FOIA exemptions to deny a requestor access to records, a letter stating the reasons for denying the records will be sent to the requestor. The letter will also notify the requestor of the right to appeal the agency's denial determination. More specific information on these exemptions and on other aspects of the FOIA program are contained in the FDA's FOIA implementation regulations codified in 21 CFR Part 20.

C. How to Make a FOIA Request

All FOIA requests must be in writing and should include the following information:

1. Requestor's name, address, and telephone number.
2. A description of the records being sought. The records should be identified as specifically as possible. A request for specific records that are releasable to the public can be processed much more quickly than a request for "all information" on a particular subject. Also fees for a more specific and limited request will generally be less. Information on major information systems maintained by the FDA can be obtained by using the Department of Health and Human Services Government Information Locator Service (GILS) site. This information may be useful in narrowing a request.
3. Separate requests should be submitted for each firm or product involved.
4. A statement concerning willingness to pay fees, including any limitations.

All FOIA requests must be in writing. The FDA does not accept FOIA requests sent by e-mail. Requests should be mailed to Food and Drug Administration, Freedom of Information Staff (HFI-35), 5600 Fishers Lane, Rockville, MD 20857.

Or requests may be sent by fax to (301) 443-1726. If there are problems sending a fax, call (301) 443-2414.

D. Fees

Requestors under FOIA may have to pay fees covering some or all of the costs of processing their request. Requestors may want to include the maximum dollar amount they are willing to pay. If the fees exceed the maximum amount stated, FDA will contact the requestor before filling the request. Requestors are generally billed for fees after their requests have been processed; however, if total fees are expected to exceed $250.00, the FDA may require payment in advance of processing.

1. Commercial Use Requestors

Search and review time: $14, $29, or $52 per hour, depending upon the grade level of the FDA employee filling the request
Duplication: $.10 per page for standard-size paper or actual cost per page for odd-size paper; $.50 per fiche for microfiche
Certifications: $10 each
Computer charges: actual cost for time involved
Electronic forms/formats: actual cost for form/format requested

2. Noncommercial Use Requestors, Such as Representatives of the News Media, Public Interest Groups, and Educational and Noncommercial Scientific Institutions

Duplication charges are issued at the same rates listed above, with no charge for first 100 pages of duplication.

3. Other Requestors, Including Consumers

Search and duplication charges are issued at the same rates listed above, with no charge for the first 2 hours of search and the first 100 pages of duplication.

Requestors should not send payment with their requests. They will be billed if the total processing charges are $15 or more. The FDA does not accept credit cards. Payment must be made by check or money order.

IX. SUMMARY

The true value of a pharmaceutical firm's regulatory specialist is largely measured by his or her success in dealing with an FDA counterpart. In the course of routine dealings with the FDA, the regulatory expert should occasionally address the following questions:

1. How expeditiously are the firm's submissions reviewed by FDA compared with other pharmaceutical manufacturers?
2. How many filings require follow-up submissions with additional data? Would adequate review prior to the initial filing have disclosed the deficiencies cited by FDA reviewers?
3. What additional steps can be implemented to speed the drug review or support process?
4. Is there an accord between the DRA department representatives and FDA personnel?
5. How difficult is it to arrange meetings with FDA staff members? Can the relationship be improved?

A knowledge of how the FDA operates is essential to the success of a DRA department. All dealings with the FDA—or other regulatory agencies for that matter—must be well conceived and adequately planned. Without knowledge, conception, planning, and an understanding of how the other half works, significant delays in drug approval frequently and painfully occur. Whether the regulatory goal is to speed the approval process for a new product or to keep a product on the market, the firm must know how best to work with the FDA. Will patience work? Should there be a legal confrontation? Should the commissioner be involved? These and other questions must be addressed and constructively resolved by the regulatory professional. Perhaps it pays to heed the words of Tolstoy in *War and Peace*: "The strongest of all warriors are . . . Time and Patience."

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Data Presentation for FDA Submissions: Text and Tabular Exposition

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I. INTRODUCTION

Over the years, representatives of both the FDA and the pharmaceutical industry have published in pharmaceutical journals or presented at workshops many helpful suggestions to facilitate NDA review of submissions and to avoid elements that impede the review. Several authors and presenters have expressed the FDA reviewers' frustration at having to review a submission that is incoherently assembled or confusing in its presentation.

It is to the advantage of an NDA sponsor to make the FDA review process as effortless for the reviewer as possible. The difference in time to approval between a difficult-to-review submission and a clear, well-presented submission may be many months, as the reviewer might require the sponsor to correct the deficiencies before the review can proceed. The marketing personnel of the sponsoring company can all too readily compute the thousands and millions of sales dollars lost for every month of delay of approval or, conversely, the revenue gained from a quick review and approval. In the worst case, a submission that might be marginally acceptable (fileable) on the merits of a therapeutic agent's effectiveness and safety data alone may generate an RTF action if errors in indexing, presentation, and assembly make a meaningful review tedious or even impossible.

The ideas in this chapter for improving the text and the tables in NDA submissions (or other regulatory submissions) will be representative rather than comprehensive and will focus more on general methods for improving the quality of the text and the tables than on specific styling conventions. Many pharmaceutical and biotech companies have their own style guides to promote uniformity and quality of documents throughout a submission. Other companies use a standard style guide, such as the *Manual of Style* published by the American Medical Association (1). Although the examples given in this chapter will be derived from the clinical area, the ideas transcend the different disciplines. Finally, it is beyond the scope of this chapter to discuss graphic presentations, which can greatly enhance the interpretation of data.

II. TEXT EXPOSITION

A. Content

Most NDA submissions contain an enormous amount of data, which cannot be presented entirely within the body of a document. Although all the data collected for an individual subject or patient (or groups of subjects or patients) may be important, critical judgment must be exercised in the selection of key data for presentation and discussion within a given document. Data necessary for the development of a specific thesis should be presented within the body of the document rather than placed into a remote appendix, which will impede the review. Less important data can be summarized briefly, clearly referenced in text, and placed in appendices. Additionally, data that have been collected over the years of a drug's development but add nothing to the evaluation of the effectiveness or safety of a therapeutic agent need not be presented at all. Any data submitted will have to be evaluated, so the inclusion of extraneous data will slow the review of the application. The submission should note the existence of such data and have it available upon request of the FDA.

B. Tone

The tone of the text should be formal without being stilted. Avoid legal language on the one hand and colloquial or informal language on the other.

C. Conciseness

Be mindful that FDA reviewers must read through many volumes of an NDA to make a report on their conclusions. Having to pour through dense, inflated, entangled text to ascertain the point being made will slow the review process. Whereas scientific data are more complex and require more effort to comprehend than most general reading material, a skillful writer will ensure that the complexity derives only from the material and not from the presentation. Wordiness and needless elaborations impede the progress of the review. Also, much of the textual data should be presented in tables to make the comparison of data easier. The following points address ways of making NDA documents more concise.

1. Keep the language simple and straightforward. Simple language is not unscientific; rather it promotes clear, fast understanding. Edit out inflated language. For example, "prior to the initiation of the study" can be changed to the much simpler "before the study began"; and "subsequent to the initial administration of study drug" can be changed to "after the first dose of study drug." Why say "The patient experienced a fall and suffered a fracture of her right hip" when "The patient fell and fractured her right hip" will convey the meaning just as well?
2. Use acronyms and initialisms to speed up the flow of text if they are easily recognized and have been spelled out at first mention. Those that may be confused with another used in the same document should be spelled out.
3. Eliminate redundancies. A careful review of the text will find many words, phrases, and even sentences that can be omitted. Sentences can often be combined by the deletion of redundant phrases, thus improving the flow of the text. Be prepared to come up against style mavens when implementing this task. For example, many "house styles" insist on units after each number in a range (e.g., 10 mg/kg–20 mg/kg). Whereas some units are brief and may not interfere with the flow of the sentence, a range such as "10 mg of iodine/ml to 20 mg of iodine/mL" would interrupt the sentence flow. This redundancy adds considerably to the length of the sentence, and the burden on the reviewer is further compounded if multiple ranges are compared within one sentence. Consider dispensing with this nicety to improve flow and comprehension.

D. Correctness

The textual presentation should agree with the tabular data in the document; in turn, the tabular data should agree with the data source (which agrees with the case report form and other clinical documentation). This is critical to the scientific merit of the submission. When lack of agreement between in-text data and source documents is found, the entire submission may be suspect, and the reviewer will be inclined to spend much more time evaluating the raw data to be sure of the conclusions.

E. Consistency

Consistent punctuation, capitalization, abbreviations, and other styling conventions are much desired in any document, but use judgment before applying the consistency rule unquestioningly. Does the adherence to consistency improve the document or confound it? For example, should all section headers at the same level have the same grammatical structure or would another structure better describe the content of the section? Be critical before insisting on consistency at any cost. A pundit once said, "Foolish consistency is the hobgoblin of little minds."

F. Clarity

The FDA reviewer should be able to read through an application expeditiously and not have to stop to try to discern the meaning of a textual presentation. The sponsor of the application should have someone who is familiar with the material in general, but not with the specific document, read it for clarity before submission. If a particular presentation is not clear to this reader, then most likely an FDA reviewer will have the same problem understanding it. Clarity is facilitated by careful attention to the following:

1. Punctuation. In *The Art of Plain Talk*, author Rudolf Flesch said that punctuation "is the most important single device for making things easier to read." (2) Omission of punctuation marks, especially commas, can force the reviewer to reread a sentence to ascertain the meaning.
2. Sentence structure and length. If long sentences are needed to report equivalent statistics that will be evaluated together, it is helpful to keep the structure of the sentence straightforward and simple. In this kind of sentence, put the thrust of the sentence at the beginning so reviewers have a reference point for the subsequent statistics as they read them. Series items should be in order, not random, and be free of interrupting material. Vary sentence lengths to avoid boredom. If possible and feasible, use active rather than passive voice.
3. Misplaced modifiers. Every style book covers this topic, but the rule on avoiding misplaced modifiers is often violated. A careful reading of the text by a good editor will eliminate this error.
4. Parallelism. Because much of the data in an NDA involves comparisons of one group to another, parallel structure is important in presenting the data. Style books for scientific writing will supply good examples of this concept.

G. Outline of Sections and Subsections

The clear relationship of one section to another is critical to the review of a document. If no definite structure is apparent, the reviewer will become lost.

The decimal system is a very popular outlining system; it is easy to use and can be set up automatically in most current word processing software applications. This author strongly advises against going beyond three or four levels in the decimal system, because it is difficult to figure out by then which level you are reading. For example, is section 3.1.2.1.2.1.1.1 on the same level as section 3.1.2.1.2.1.1 or is it a subsection of the former? If no other formatting characteristics identify the subordination of one section to another or are not recognizable as clear distinctions (e.g., all caps, bold versus initial caps, bold), the reviewer has difficulty figuring out the relationship of one section to another. This is also true of another popular outlining system, the alphanumeric system, where letters and numbers alternate as section headers. After a few levels, the distinctions become obscured, and reviewers will become lost.

H. Indenting

Avoid indenting large sections of text. Most text should be flush to the left margin with appropriate headers to identify the section. Multiple and sequential indenting wastes space and is confusing. Short lists are appropriately indented, and conventions like indenting with bullets are useful to break up long sections of text.

I. Global to Specific

For any section, begin with global statements or data and then discuss the specifics. For example, in the discussion of adverse events, the overall presentation of the events should precede the presentation by severity, by relationship, by subgroup, etc. It is particularly important in the discussion of the populations evaluated in a particular document. Begin with the all-inclusive population first, then define the subpopulations. One NDA this author worked on had about 10 different populations, many of which were close in numbers of patients (e.g., all patients entered, all patients treated in controlled studies, all patients treated in uncontrolled studies, patients treated with test drug in controlled studies, patients treated with active comparative agents or with placebo in controlled studies). This caused great confusion until a table was constructed to identify each population, beginning with the largest population.

III. TABULAR PRESENTATION

In-text tables should be used whenever they simplify the presentation and allow for substantial reduction in text. Comprehensive multipage tables that interrupt text should be avoided, if possible, unless they are critical to the development of the thesis of the section. However, if the tables are very important, they can be placed in the same volume in an appendix. Usually, data can be collapsed to be included in the in-text table, with reference to the full table in an easy-to-locate appendix. It should be mentioned here that any tables, figures, or graphs in the appendices must have in-text references.

Information from the tables should not be repeated in the text except as part of a concluding statement about the tabular data or trends seen in the data. The commentary on data from the tables should precede the table, beginning with an introduction to the table by number and a statement identifying what type of data it contains. Additional commentary related to the table but not derived from the tabular data may follow the table.

A. Title

All tables require concise but descriptive titles. Sequences of tables that are similar should identify their differences very conspicuously in the title, such as at the end of the title after a colon (e.g., Treatment-Related Adverse Events: by Age; . . ..:by Sex; . . .:by Race).

B. Data Source

Every table should identify the source of the data contained in it. This is usually done in a footnote to the table (e.g., Data source: Statistical Table 23, Volume XX, p. xx). The volume and page numbers will be inserted at the end of the project. Exact referencing of in-text tables will facilitate the review process.

C. Footnotes

Footnotes should be assigned letters (superscripted), not symbols or numbers, which can be confused with the data. Asterisks (*, **, ***) are generally reserved for levels of statistical significance. In multipage tables, footnotes should be assigned letters in the order in which they appear on the specific page of the table. Always begin such tables on a new page to avoid changing the footnotes as the tables shift with the addition of preceding text.

D. Orientation

Portrait tables are always preferable to landscape tables. Remember that the volumes in a submission will be about 2 inches thick. It is cumbersome, annoying, and disruptive for an FDA reviewer to have to move the volume around repeatedly to coordinate the text presentation with the tabular data. If data appear not to fit in the portrait orientation, try changing the axes of the table, so that the axis with more individual descriptors is vertical, whereas the axis with fewer items is horizontal (column headings). Also consider revising the table into separate sections under the same column headers, with descriptive headings for each section spanning the width of the table.

E. Order of Data Presentation

In multiple tables with similar data, present the data in the same order as much as possible. If the first column always has the active drug and the second column the placebo or comparative agent, then keep this order throughout the tables. In the analysis of data by demographic or disease subgroup, it is helpful to keep the subgroup of concern (i.e., women, the elderly, racial subgroups, impaired renal function) in the same column in each table.

F. Present Meaningful Data Together

Try to present the data that will be evaluated and compared as close together as possible rather than scattered around the table. For example, if the tabular data represent both evaluable and nonevaluable patients who have been either previously treated or previously untreated, place the evaluable patients together rather than present them by previous treatment.

IV. CONCLUSION

The suggestions presented in this chapter for improving text and tables are meant to be neither complete nor sacrosanct, but simply considered. Indeed, the suggestions may be countermanded by particular constrictions and style conventions of the company sponsoring an NDA or other submission. However, the ability of the writer to look at a document through the eyes of an NDA reviewer will reinforce the suggestions in this chapter. The goal is to speed up the review process and obtain fast approval for a new drug entity. Any suggestions that facilitate this endeavor should be welcome.

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The Computer World in New Drug Development

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I. INTRODUCTION

The first edition of this book included a preface that began "... to help reduce the time required for a new drug or antibiotic to gain marketing approval." This statement helps summarize the goal of computing in new drug development. The cost of bringing a drug to market is staggering. One must factor in the costs of developing a drug, the percentage of drugs that actually are approved, and the time to achieve a marketable product. By leveraging technology to allow individuals and groups working together to be more productive, one can reduce the time it takes to reach conclusions about these developmental products. With estimates of the true cost of drug development reaching into tens of thousands of dollars per day, reducing the time to market by even a month can reap huge benefits. These potential cost savings can easily help justify the expense of computer technology. Because studies are becoming more complex and more expensive, applying technology becomes critical for the effective management of the development process.

This chapter will describe networking technology, hardware, and some of the software that are used for the clinical trials and regulatory phase of new drug development. The technical side of computing will be avoided; instead, general terms will be discussed. Because technology evolves rapidly, a look at emerging technologies, such as the Internet, is in order, along with a brief history of technology. Software will be discussed in terms of general applications, that is, those that apply to all industries, and vertical market applications, which are specific to the drug industry.

II. USING COMPUTERS TO WORK TOGETHER

Teams of people using computers together is the key to leveraging technology to get complicated jobs done quickly and effectively. To understand the concepts of workgroup computing, it is important to understand how this technology evolved from individual computers. Only a decade ago, large companies used large systems or mainframe computers. Small companies had no systems. The large systems were expensive and difficult to maintain, but resources were shared effectively and centrally controlled. These machines did not increase personal productivity or enhance the work flow of an office or team, but rather helped companies do batches of work more quickly. This was great for printing bills or doing data analysis. With the wide acceptance of the personal computer, this paradigm shifted. The power to compute was put into every user's hands, and information no longer "belonged" to the few people in the information systems department. Information could be entered, manipulated, and reported by the people who actually used it. This computing revolution is still going on, and over the past few years, we have been seeing the elimination of mainframe computers in favor of smaller networked systems.

The personal computer has drastically changed the way individuals work. The power of the machines on our desks has doubled and tripled every few years. This trend should continue for some time, and there will be many new developments in the future. The box sitting on top of a user's desk unleashed the individual's potential to create. However, a single computer helps only one person work. Just as a single person could not take a new drug from concept to marketplace, a single computer is not a solution by itself. People are most productive working as teams, and by teaming the computers together into a network, they can now work effectively as a group. The power a user has on the desktop is extended to the workgroup, the enterprise, and even business partners and customers. The sharing of resources, the hallmark of mainframe computing, is applicable to the workgroup through the network. Unlike mainframe systems, the network allows the individual, not someone in the systems department, to control the resources.

A. Networking

In general terms, a network means that computers are connected together to allow resources to be shared. At the very basic level of networking, the computers share files and printers. File sharing is the storage of files in a common place that lets multiple users access the same information. This seemingly simple concept implies that there is only one copy of the work that everyone can share, without having to worry about consolidating the changes that everyone makes had they been working individually. Printer sharing saves money, in that a company does not have to purchase a printer for every user. These two concepts, as simple as they may be, are the foundation of more extensive networking services.

Networking provides many other resources. Two of the most important are electronic mail (e-mail) and shared databases. Electronic mail, which is becoming ubiquitous in the workplace, enhances the ability of users to work with each other and instantly send information to those who need it. A document can be sent around the world in minutes. Unlike regular post or fax, e-mail gets the information to the end user in its original form. The end user does not need to retype the document to edit it. Hence, the document can be revised and returned via email. E-mail, coupled with file sharing, is the simplest form of workgroup computing.

With the addition of a shared database to a network, users can now centrally store data, find the data again easily, and report on it. The network extends the database to all users who need the information. Information that is changed by one user is instantly updated for all users. As new information is added to the database, all the users can see it. With a modern database, it is important to note that the data contained within the database need not be limited to plain text data. Text, images, documents, video, sound, and any other information that can be entered into a computer can be stored in a database.

B. Groupware

When all of these services were combined, a new class of software emerged—groupware. Groupware uses all of these concepts to build software that lets teams of people work together using computers. File sharing lets users give others access to the information they have created. Electronic mail lets users send this information to others quickly and easily. Databases allow users to store their work in an effective way so that others can update and change information as needed. With all of these services together, workflow can be enhanced to get a job done quickly.

As an example, we can look at how data for a clinical study would be entered without networking and groupware applications. First, data entry screens would be designed and copied to a disk to be distributed to the computers where the data entry was done. The data would be entered and copied back to a disk. The disks would then be collected and merged together at some computer. The data would then be analyzed for correctness and completeness. If problems were found, the problem would be relayed back to the data entry person responsible for the problem (by a phone call, memo, or post), the work rekeyed and then re-collected and remerged. When the data entry was complete, it would be copied and handed to others for statistical analysis.

The same scenario in a workgroup would go something like this: the data entry screens would be designed. Because the data entry system is on a network, all of the computers where data entry is done would instantly have a copy of the screens. This is file sharing. Data entry would begin. The data are entered into a common database and are already merged because they are entered in a common place. Data are checked for errors while the entry is being done, because the data administrator can view the data being entered. Here we can see the value of shared databases. If a problem is found, it does not matter who entered the original data, as these are all in the same place—a common database. The problem can be corrected by anyone, because everyone has access to all of the information. The details of the problem are e-mailed to the person entering data. The problem is fixed, and the data collection is finished. However, the group that does the statistical analysis did not have to wait until the data collection was finished before beginning the analysis. Because the data are shared, the statisticians can start programming with preliminary data, saving time.

With this simple example, the power of groups using computers makes itself apparent. People can work together, save time, and be more productive. There is, however, a single technology that extends the power of groupware infinitely. Suppose we could extend the group of people we work with on computers outside the department or company we work for? What if we could extend our workgroup with the business partners and customers we have? A few years ago, the only way to do this was to build a private network, which was very expensive, considering the communications costs. Today the Internet provides these services. Intranets and extranets provide similar capability, but only to those a group needs to work with.

III. THE INTERNET

The Internet, heard about almost everywhere in print and media over the past year, is actually a simple concept. There are many computers in the world. If all of the computers in your company are connected together, you have a network. If all of these networks around the world are connected, you have a very big network. This is the Internet. Because a company pays only for its connection to the Internet, the need for high cost private networks begins to disappear. An office in New York can communicate with the Los Angeles office for the price of two local Internet connections.

Only a few years ago, a company would have to consider the cost of a leased telephone line between the two cities to network the two offices effectively. Much information transferred between sites in this scenario is sent in bursts, that is, a bunch of information is transferred at once, and then there is no information for a while. This is typical of electronic mail and file sharing. The line might be busy during the day but dormant at night. By using the

Internet to transfer information, an organization pays only for the local connections. The long distance connection is already provided. Consequently, the Internet leverages the existing communications infrastructure of the world for the benefit of those attached to it.

Besides being a way to transfer information quickly and cheaply, the Internet provides a standard set of protocols for communication on it. Software developers use these protocols to ensure that different computer systems can communicate effectively. This is a problem solved for workgroups that need to communicate with other companies. Even though the workgroups might be using different systems and software, the Internet provides a standard way to get data from one place to another. One of the most basic services the Internet provides is a means to transport e-mail outside of one's organization to other organizations. With this digital "highway," information can be sent quickly from place to place. Electronic mail arrives around the world in minutes.

Perhaps the most universal application on the Internet is the world wide web. Some background is needed here. Many people have a need to publish information that is useful to others. Knowledge could be transferred easily if a computer user could put a document in a place where it could be accessed by anyone in the world at any time through the Internet. It would also be worthwhile if references in the document to other works also published on the Internet could be linked. Thus, a user reading the original document could simply select a link and instantly see the referencing document. If you were to sketch a picture of all these documents as dots on a page and draw lines between them to illustrate the links to references with these documents, you will draw a web. Because these documents are published all over the world, we have the world wide web.

A. Intranets and Extranets

So now a workgroup has a way of transferring information quickly, easily, and inexpensively on the Internet. There is also a way of publishing information in a way everyone else can see it. These electronic documents contain links that will transfer the user to other pertinent information quickly. This is a powerful concept. If, however, we limit our view of the world to the workgroup we work in, we have an inTRAnet. The value of the Internet and all of the problems it solves has been leveraged to help a workgroup process information. An intranet is usually company or department wide, allowing users to collaborate quickly and easily by providing to a few users the powerful tools the Internet provides.

At times it may be ideal to extend the workgroup to others. The other users would be colleagues at partnering companies, vendors, or customers. If we extend the concept of an Intranet to these people outside our workgroup, we have an extranet. Information can flow to all those who need it. Security on computer systems makes sure that only users with proper credentials gain access to information.

Because the Internet extends the workgroup to the world, users can work anywhere. Telecommuting lets the members of a team work from a client office, from a clinical site, or even from home. Users can physically be where they need to be while accessing up-to-date information from wherever the information needs to be. For example, suppose your organization is contracted to manage remote data entry, and five sites are set up for data entry. Without the Internet, the data are entered and transferred from each site by a direct connection to the home office. The cost of the direct connection is based on how far away the sites are from the home office. Each site has to manage the communications link. The home office has to manage five communications links. When the data are transferred to the home office, they are copied on disk and sent to the customer for whom you are providing data entry services. The communications are expensive. With the addition of the Internet as a business component, each site would have a local connection to the Internet, providing inexpensive communications. The home office would also have one connection to the Internet for ease of management and lower cost. The Internet infrastructure would pick up the high cost of communications, inasmuch as all users of the Internet would share the lines. Because your customers would also have access to the Internet, your organization could extend access to the data collected to the customers by building an extranet. The customers would have instant access to the data, allowing them to continue their work without waiting for data transfer.

Let us take the example above one step further. Suppose the data being entered are feedback from patients on their experience with a new drug. If the data entry forms are provided as a world wide web document, the data entry could be done by the patients themselves. Patients with local access to the Internet could simply call up the web document on their computer. Patients without computers could have an inexpensive device hooked up to their television to allow them to do the data entry. Because the data are entered through the Internet, they are instantly sent back to the central office. The data are stored in a shared database so that the data management personnel can quickly and easily track them. The biostatistics workgroup can start working on statistical analyses. The clinical department can monitor the progress of the study. The client can have instant access to the data at all times.

Over the last decade, computer users have extended their environment from the desktop to the network. The network has been extended by workgroup applications. Over the past several years, the workgroup has been extended to include all the other computers in the world through the Internet! The key to success in deploying technology is leveraging the resources of global networking to help teams accomplish their job quickly, easily, and inexpensively.

IV. SECURITY AND QUALITY ASSURANCE

The pharmaceutical industry has some special requirements of the systems that help bring new drugs to the marketplace. As previously mentioned, the focus of technology is to help bring a new drug to market more quickly, thereby reducing costs. Two important considerations must be made here: security and quality. In a perfect world, everyone, including your competitors, would work together and everything would always work properly. Anyone who ever had a computer crash and lost an important document knows that this is not a perfect world.

Connecting computers to allow individuals to work together is effective only if the proper security is in place to ensure that data are not tampered with. For example, once data entry on a project is completed, the users analyzing the data should not be allowed to change the data. Although the change might be convenient, it might not follow the protocol defined in a study. With the staggering amount of information generated in an NDA, it is also important to know when and where a document was modified and by whom. Proper security allows an organization to prevent a problem before it starts. When a workgroup is extended over the Internet, security becomes paramount. Data are in effect being transferred over a public network. Sending data on the Internet is much the same as standing on the roof of your building and yelling through a bullhorn. Everyone who is interested could listen. Confidential patient information could be compromised. Securing the data transfer with encryption is a simple solution.

Moving data around, even if the data are secure and can be seen only by the proper users, is worthless if the data are incorrect. Validation of computer systems is key to ensuring that data are correct and that the desired output of a system is the actual output. Software developed to assist in new drug development must perform flawlessly. Just as machines that produce the drug itself must be validated to ensure quality output, so must software used to produce the data used in proving the efficacy of a new drug. Custom software targeted for the drug industry should be rigorously validated to ensure quality.

V. HARDWARE

Perhaps the easiest choice to make in defining computer requirements is the hardware. Many people may disagree with this viewpoint. There are dozens of choices of popular hardware platforms, depending on the size of your business or your personal preference. The hardware is, however, not important. The software runs your business. Defining the software that will be needed to do a job is the hard part. Once the software has been chosen, the hardware requirements of the software define the hardware needed.

For networked computers, two types of machines exist—servers and workstations. Servers should be as powerful as the budget permits. These machines are used by all users, and this fact alone should justify their need for power. Workstations should be purchased with similar logic. Even though only one person uses a workstation, it is important to have computers powerful enough to do the work required of them. Many professionals in the drug industry demand high compensation for their services. A user left waiting for a machine is unproductive. The extra cost of a more powerful computer is often well justified if it can help such an individual be more productive.

VI. SOFTWARE

A. General Software Applications

Applications software that is not targeted to a particular industry is termed "horizontal" because it fits into a wide range of industries. The basic group of software is the office suite of applications, consisting of a word processor, spreadsheet software, and e-mail. The suite of applications is generally extended with presentation, database, and Internet software. Given that vendors deliver these applications together, the data can flow between them easily. For example, raw data in a database can be called into a spreadsheet and analyzed. The resulting analysis can be merged into a word-processed document. The resulting document can then be sent by e-mail to its intended audience, or posted on the Internet, intranet, or extranet for review. The key to choosing applications software is that it provides the feature set that is needed in your organization. It is also important to ensure interoperability with all the users in your organization and customers, if needed. Although basic applications software from vendors often can read other vendors' data, problems can arise. What looks perfect in one word processor can be incorrectly formatted in another. The most popular suites of desktop applications software currently are Microsoft Office^{TM}, Corel Word Perfect Suite^{TM}, and Lotus Smart Suite^{TM}. Each suite of software provides the rudimentary services expected, but works differently in groups.

Software used to extend the desktop computer to the workgroup is groupware. At the base level, e-mail systems extend the desktop software by allowing users to send documents to each another. However, such a system can be seen as a large database that holds information. After all, a mail message is just a document in the first place. Because mail systems are repositories for information, software providers have extended their scope to manage many group tasks. Most current mail systems provide a way to do group scheduling, contract management, document management, and electronic forms. For example, a document created in a word processor or spreadsheet program can be "stored" in the groupware system, where it is indexed and cataloged. Changes to the document can be tracked through an audit trail maintained by the groupware system. The documents can then be routed by e-mail to other users for feedback on content, being tracked at every step. A user who sees a need to address an issue in the document could schedule a meeting electronically. The document could be marked up and sent back to the author, and changes could then be incorporated.

Popular groupware systems include Microsoft Exchange™, Novell Groupwise™, and Lotus Notes™. Each system has advantages and whereas each will work with all software suites, it works particularly well with the office suite application that is marketed along with it. The pioneer of groupware was Lotus Notes. Exchange and Groupwise are, however, quickly becoming popular alternatives in the arena of groupware previously dominated by Notes. The key characteristic of these systems, as opposed to simple e-mail systems, is that they include and ride on top of a database. The database is the repository of all data stored in the groupware system. Electronic mail systems only send information from one place to another. The data are not stored anywhere for "public" use. However, in true groupware systems, the database stores all the information, which can be displayed to all users who need it. Because the database can store other information besides e-mail, the systems can be extended to do document management, collaboration, and work flow applications.

A perfect example of groupware would be a system to track an ISO-9000 application. Achieving ISO-9000 certification involves creating a large set of documentation on the quality procedures of a company. The documents must be maintained, revised, and controlled centrally. If updates are made, they must be tracked. When changes are made, they must be approved. Creating a system to manage this in a straightforward file-sharing network would take a great deal of manual organization. A groupware system provides all of the facilities needed. It can be set up to store documents centrally, manage distribution, track where documents are for approval, and allow consolidation of changes. The documents never actually leave the system. All users share the information from a central repository.

The last horizontal application to be discussed here is the database. Although most of the desktop applications include a database, another class of database software exists—the database server. The responsibility of this software is to manage all databases on a network in a central location. The application software on the user desktop can then access this database. Database servers are not used in and of themselves; they are often the platforms on which other systems, particularly vertical market systems, are built. The advantage of using database servers is that the server generally resides on a powerful computer, giving users fast access to the data they need. Some of the most popular database servers on the market include Oracle™, Microsoft SQL Server™, and IBM DB2™.

B. Pharmaceutical Specific Software Applications

1. Data Entry and Verifications Software

Studying a new drug generates a great deal of information, all of which must be captured from patients in a clean and consistent manner. The accuracy of the data is very important. After case report forms are completed, they must be entered into a computer for data analysis. The data entry system allows a data manager to design data entry screens that generally mimic the design of the case report form. The data entry operator then fills in these screens. The data entry system usually has the capability of rudimentary data verification on input. The individual fields of data often can be programmed to accept only valid ranges of input or be validated on the basis of the input given for other fields. Dates and times can also be verified automatically. The goal is to limit the number of errors allowed.

Often, a single data entry still will be prone to errors. The data entry system will allow for a double entry of all information. The same operator who did the original entry should not perform the second entry of the information. The data entry system can resolve inconsistencies two ways. During the second entry, the system will show mistakes as they are typed, asking the operator to choose which version is more correct, the first or second. The system may also run in a batch mode that compares the two entries and prints a report of inconsistencies. The operator can then go back and choose the correct version.

The final aspect of the data entry system is its ability to make the data entered available in a format that can be analyzed. As the data entry system probably has no facilities for analysis in and of itself, the data must be exported to a system that can do the work. Some standard exports are to SAS datasets, SQL databases, and plain text, which is usually a common denominator among applications software. The data are then used in that format or converted to an internal format for analysis.

2. Case Report Form Design

A case report form is similar to any other form that is specific to the clinical testing of a new drug. A form is made up of descriptive fields and empty space to fill in the data. Design of the case report form can be done by hand or on a typewriter. Designing the form on a computer will allow it to be easily changed and adapted for different studies. Data entry systems can be used to design the case report form but often lack the flexibility to go to print, as the system is designed to create computer screens, not hard copy. Many different software packages can be used for the design of these paper forms. Word processors and drawing programs are popular systems for form design; form design packages also exist. Word processors are excellent for entering the text of forms, but are often lacking when it comes time to draw boxes, lines, and symbols. Drawing programs are the opposite. They allow the designer to easily create graphics but may make it difficult to manipulate the text and instructions on the form. Form design software tries to give the user the best of both worlds. The text on the form can be easily added while also allowing for graphics and fill-in parts of the form. Some form design packages also have a runtime version that can be used for data entry. The runtime software cannot be used to design forms, but it can display the form on a computer screen and allow data to be entered. These systems generally do not have a facility to verify data by double data entry.

3. Automatic Data Collection

Doing data entry is tedious, and operators are prone to error. Because all the data must be typed into a computer, it is time consuming. Double entering the data to find mistakes takes twice as long. Having a data entry operator enter data into the computer from a case report form is redundant, as the data were already entered once, on the case report form itself. Automatic data entry systems solve these problems by capturing data as they are entered. A patient might enter responses directly on a computer system or use voice response telephone technology. Specialized hardware can be given to a patient for input that can be taken directly and downloaded at a later time. This hardware can be a handheld device that records patient feedback or a personal computer that displays a form for patient input. The data can also be collected on the Internet, with a case report form created as a world wide web page. The screen is filled in and instantly sent to the group doing data collection.

If a case report form must be used, the form can be scanned or faxed into a computer system. This form is then read using optical character recognition (OCR) and converted to raw data. The accuracy of OCR applications is high, but the data must be checked to ensure quality. The OCR software can have problems with ambiguous data. For example, the letter "l" and number "1" can look the same on paper. The elimination of the data entry step saves both time and money. Careful design of the case report form and good instructions to the end user will minimize entry errors.

Moving the data from the point of capture to a database for analysis is a caveat of remote collection. Once the data have been captured, they have to be sent to a central database before analysis can begin. Movement of the data should be both reliable and inexpensive. Building a private network to accomplish this can be expensive, but newer technologies are driving this cost down. Many organizations are taking advantage of the Internet as a way to transfer data quickly and inexpensively. Networking companies such as AT&T™ and IBM™ also offer global networking services to allow distributed sites to communicate with a central database.

4. *Autoencoders—Adverse Events and Drugs*

Perhaps the most tedious aspect of data entry is being sure that the drug names used and adverse events reported use the proper medical dictionary term. The key reason for this is proper analysis of the data when it reaches a biostatistician. To properly query data and find correlations between variables, the data must be consistent, in that the same drug name or adverse event is described the same way. Dictionaries classify drugs and events so there can be no ambiguity during data analysis. Various reference texts, such as the WHO™, COSTART™, and ICD9™ dictionaries are available. Browsing and manually coding the data can be a tedious and time-consuming process. The person doing the coding must search the data while referring to the dictionary. The job of the autoencoder is to do this automatically. Given a set of data, the software will scan the information, look for terms that are not in the dictionary, and replace them with the preferred term. The software accomplishes this by having knowledge of base terms matched to preferred terms. The software then goes out and searches for base terms and provides the proper preferred term. As terms are used, they must be added to the knowledge base so that the system will recognize them in the future.

5. *Adverse Reactions Data Base*

A drug must be monitored for adverse events. This monitoring can take place in both the pre- and postmarket use of a drug. The data returned must be kept in a database for tracking and reporting. They should also have audit trails attached to track changes over time. Because there are global reporting requirements from WHO for adverse events, the software usually will be packaged with predefined reports to satisfy regulatory organizations.

Autoencoders are a unique and specialized class of software. One must remember that coding is a means to an end. Data consistency is the desired result. For this reason, companies will use different dictionaries and methods to code adverse events and drugs. There is no standard other than the dictionaries used for the process. Autoencoders are usually custom systems developed by a company for its own use. Commercial autoencoders do exist, and they generally provide facilities to audit the coding and provide custom dictionaries based on the general dictionaries above.

6. *Statistical Analysis*

Once available data have been captured, they are turned over to the biostatistician for analysis. Many systems exist for this purpose. Because statistical analysis is not specific to the drug industry, there are many off-the-shelf packages available. Rudimentary work even can be done with an electronic spreadsheet.

In new drug development, the de facto standard is SAS from the SAS Institute. SAS is a flexible system designed to be used in an interactive or batch mode. It also has the flexibility to read data from many sources, including database systems, making it a good choice for integration with other packages. Many software developers even use it to develop some of the other software discussed here, such as trials management and CANDA systems.

7. Validation and Change Management

An important aspect of using software in drug development is ensuring that the application works properly. Given a certain set of input, the software needs to produce the correct output, and the software must be thoroughly tested to ensure this. Validating software is complicated by the fact that software is dynamic. Vendors constantly improve applications. When new features are added, the software must be revalidated. Changes in the system must be well defined, managed, and tracked through the application. This is especially true of software suites, where applications are shared and work together. A problem that does not appear in one program might produce incorrect output when modules are used in another program.

8. Document Management/Acrobat

Developing a new drug leads to a great deal of documentation, compounded by doing an FDA application. Managing the documents can become a significant task. Just finding documents can be difficult if a user does not know the location of the file on disk. In some cases, documents also need to track revisions and an audit trail of user modifications. Facilities exist in most current word processors to do rudimentary audit trail functions and to track changes to documents. A document management system enhances these capabilities. The systems work by using a library approach to documents. New documents are created and checked into a library under an appropriate heading or study name. These documents are then checked out as users need to modify them, and this transaction is logged. This approach ensures that only one user can modify a document at a time and that an audit trail exists. Security can be set up to define which users are allowed to change documents. Upon completion, a document can be locked to disallow further changes. Document revisions can be kept to track history. The document system also generally provides an index of documents in the library. Through the index, a user can quickly search for documents with specific contents. This is especially useful for a large workgroup in which one individual cannot possibly know the content of all documents within a project.

Case report forms, drug complaints, and adverse events are also documents that should be managed. These can be kept in such a system for all of the same reasons word processing documents are kept there. By keeping an index of the contents, fast answers to queries can be gained by the central storage of these necessary records.

One problem with documents kept in any system is that other people given the document will need the same application to view the document. Sending a file in Microsoft Word format requires that the recipient also own a copy of Microsoft Word. Without it, the document cannot be viewed. This problem has been solved by a new standard known as Acrobat™ from Adobe systems. By using Acrobat, anyone wishing to publish a document uses the Acrobat™ software to create a version readable by the Acrobat™ Reader. The reader software is freely distributed, so the recipient of a document need not buy a copy of the original software. Besides being able to create documents viewable by anyone, this new standard also allows the document to be indexed. Any part of the document can also be cross-referenced to other sections. These features are especially useful in documentation, particularly in NDA submissions. Volumes of paper documents can now be stored on a single disk and instantly cross-referenced. A reviewer could have an entire NDA available on the computer screen.

9. Trials Management Software/CANDA Systems

Clinical trials management systems attempt to roll many aspects of the clinical process into a single suite of software. Like the "office suite" of applications, trials management software is a one-stop-shop. The software provides such services as trials planning, management, monitoring, data entry, and reporting. The fact that this software tries to do all the work needed for a trial implies that significant management and maintenance are required just for the software to run. This fact is justified, however, because the software allows a large workgroup to work together effectively. This class of software usually runs only on specific computer systems and is often high priced. A database system is often required for the software to run, as it keeps all of the data in such a system.

The advantage of this type of system is scalability. A study might involve many people, and the management software effectively links their work together. By empowering a workgroup to concentrate on complex studies together, the end result will be a significant time saving, leading to cost saving. One problem with these systems is that because they try to be all encompassing, they might not be the best solution for a particular task. The benefit of a trials management package must be judged against the benefits of stand-alone software packages that also provide the same functionality.

Computer assisted new drug applications are a class of software that helps users take a drug through trials to application. These CANDA systems generally offer many of the features of trials management software, but assist in the reporting and document generation required for applications.

10. Internet

The Internet has revolutionized the way information is delivered to computers. A whole chapter could be dedicated to the current and emerging technologies and their applicability to the drug industry. Besides the wealth of information available, the Internet also provides quick and inexpensive transfer of data.

Linking the internet with other technologies previously discussed provides a powerful way of sharing information. As applications start to take better advantage of the Internet, limits of location and distance start to disappear. Users in different parts of the world can communicate as effectively as users in different cubicles.

VII. CONCLUSION

As time goes on, new technology will improve the efficiency of people working together to create new drugs. Software vendors have solved many of the problems specific to the industry. Technology will become more important to make studies manageable. Users must overcome fears of change and embrace technology. Because of the rapid changes taking place in computing, users must also stay aware of emerging technologies and determine if these new technologies make good business sense to improve the speed and efficiency with which new drugs are brought to market.

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Working with a CRO

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PART I. CONTRACT RESEARCH ORGANIZATIONS

I. INTRODUCTION

The use of CROs in nonclinical and clinical drug development programs—or "outsourcing," as the process is commonly referred to by the industry—is a common practice of many pharmaceutical and most biotechnology companies. At present, more than 450 CROs exist in the United States and Europe, and the use of their services for all aspects of the drug discovery and development process is rising. The growth of outsourcing is expected to continue, with some CROs offering a complete drug development support system, from synthesis and characterization of the drug substance to conducting phase 3 safety and efficacy human trials, and preparing NDA documents for submission to regulatory agencies. Other CROs specialize in selected aspects of the drug characterization process, offering services in such areas as pharmacology animal model development and implementation, formulation development and drug product stability testing, bioanalytical method development and validation, or clinical trial protocol preparation and study support.

This chapter discusses the processes commonly used to select a CRO for the nonclinical and clinical biological stages of drug development and the requirements for obtaining an appropriately completed study at a CRO. The processes and requirements for outsourcing the manufacturing program for a drug substance and the preparation and testing of a drug product are also areas of high growth, and a number of CROs offer these services. However, the outsourcing of manufacturing processes, including the preparation of the chemistry, manufacturing, and control section for regulatory submissions, is not covered in this chapter.

II. NONCLINICAL CONTRACT RESEARCH ORGANIZATIONS

A pharmaceutical or biotechnology company identifies a lead candidate that mediates a human disease and then conducts the required, GLP-driven preclinical research studies to obtain an IND, followed by the nonclinical and clinical studies necessary for an NDA submission. For several reasons, corporate management may decide to have some or all of these studies performed at a CRO. The drug development project team is informed of this management decision and is usually given the responsibility of coordinating the outsourcing program, as well as the internal research studies, and of ensuring that the development program stays on time and on track. For a small biotechnology company, this responsibility may fall on the shoulders of a single individual or a small group of two or three researchers, who need to have a good understanding of each of the scientific disciplines for which outsourced studies are being considered. A common practice for many biotechnology firms is to contract with a consultant or a consulting firm to assist in outsourcing.

The first requirement for a successful program at CROs is to identify which research studies or aspects of the nonclinical drug development program are to be conducted at a CRO. Then, the projected timeline for initiation and completion of the studies are needed so that results and technical reports are available at the appropriate time for decision making and regulatory agency submissions. As discussed in the chapter on project teams, a well-constructed drug development plan provides much of this information. The project team members whose scientific disciplines are part of the outsourcing program are typically assigned as scientific experts, and the project team coordinator is given responsibility for contractual arrangements. These subproject teams need to first identify and then select the appropriate CRO or CROs to conduct the desired research studies. These teams also need to monitor the CRO(s) to ensure that the studies are being conducted as designed and described in the study protocol and that the generated results are appropriately recorded in both the study records and the study report. The following sections provide more details on the CRO selection and monitoring processes for nonclinical drug development research studies.

A. CRO Identification and Selection

After a pharmaceutical or biotechnology company, commonly referred to as the sponsor, has decided to use CROs to support some of the nonclinical research effort in a drug development program, management or the project team responsible for the development of the drug candidate assigns individuals to identify and select the appropriate CROs. The steps in a selection process should include, but are not be limited to:

1. Preparing the study designs for each of the research studies to be contracted. The more details provided in the study designs, the better. The CROs use the provided information to prepare a draft study protocol and a proposal with time and cost estimates. Examples of two study designs are shown in Table 1.
2. Determining which CROs should be considered as potential contractors. This aspect of the selection process is discussed in more detail below.
3. Soliciting cost and time proposals for each study design from each CRO. Generally three to five CROs that have the necessary expertise to complete the study successfully are requested to submit proposals for each study design.
4. Evaluating the proposals, which includes determining if the CRO understands the study design, and selecting those CROs to be considered further. At times, CROs will recommend additions to the study design, which may or may not improve the overall study and could provide additional information for the complete characterization of the drug candidate. When this occurs, the sponsor needs to critically evaluate the expanded study and determine if the increased costs and, possibly, extended study duration justify the additions to the study design.
5. Scheduling and conducting site visits to ensure that the CROs are qualified and have the facilities and personnel necessary to conduct the research studies. These site visits include assessments of GLP compliance, SOPs, and computer validation.
6. Negotiating time and cost for completion of the research studies. The original estimate in the proposal is usually not the final cost of conducting a research study at a CRO. Those CROs still on the short list should be asked to provide their "best and final" cost, the dates they can actually initiate the study, and the date they project the draft final report will be available for review. Some firms specialize in this phase of interacting with CROs and will negotiate with the CROs for the sponsor, thus relieving the sponsor of the problems that can occur by pushing for the best price. As payment, these firms receive a percentage of the difference between the original estimate and the final bid. The difference between original and final bids can be large, sometimes hundreds of thousands of dollars, for some studies such as carcinogenicity testing.
7. Selecting the CROs and awarding the contracts for each study to be outsourced.

The number of person-hours required for the identification and selection process depends on the size of the research program to be contracted. Normally, a minimum of 1–2 person-weeks is necessary to evaluate three to four CROs

Table 1 Study Design Examples for Contract Research Organization Time and Cost Proposal Preparation

28-Day Toxicology in a Nonrodent Species

Purpose: To evaluate the toxicology of a protein test article in a nonrodent species after every-other-day subcutaneous dosing for 28 days.

Test Species:	Beagle dog
Test Article:	Protein therapeutic
Dose Levels:	300, 100, 30 and 10 μg/kg plus vehicle control
Frequency:	Every other day (EOD), 14 doses total
Administration:	Subcutaneous, bolus injection; duplicate aliquots of each formulation collected predose and postdose for the 1st, 7th, and 13th dose to be analyzed for test article concentration
Number:	Three animals per sex per dose group with four dose groups and a vehicle control group (30 animals total)
Evaluation:	Clinical signs of toxicity during in-life phase including general health, body weight, food consumption; clinical pathology (hematology, clinical chemistry, urinalysis) predose, after 4th, 7th, and 14th doses; gross pathology including selected organ weights; histopathology
Toxicokinetics:	Blood specimens collected after the 1st, 7th, and 13th dose to be analyzed for test article concentration to assess extent of exposure
Antibodies:	Blood specimens collected prior to the 1st, 7th, and 14th dose to be analyzed for antibodies to the test article
Timeline:	Projected start date Estimated completion date

Absolute Bioavailability, Pharmacokinetics, and Dose Proportionality in Nonhuman Primates

Purpose: To evaluate the absolute bioavailability and pharmacokinetics, including dose proportionality, of a small organic molecule drug candidate in a nonhuman primate.

Test Species:	Monkey, Rhesus
Test Article:	Small organic molecule, molecular weight less than 350
Route:	Intravenous, 100, 30, 10, and 3 μg/kg (or other dose range) Oral, 1,000, 300, 100, and 10 μg/kg (or other dose range)
Frequency:	Multiple using balanced, crossover design with 7-day washout period between doses
Administration:	Intravenous, slow bolus injection at about 1 ml/min Oral, gavage Duplicate aliquots of each formulation collected predose and postdose to be analyzed for test article concentration
Number:	Equal to number of doses in crossover design
Specimens:	Blood for plasma; sufficient number to characterize the absorption, distribution, and disposition phases of the test article

Table 1 Continued

Absolute Bioavailability, Pharmacokinetics, and Dose Proportionality in Nonhuman Primates	
Possible series:	0, 5, 10, 20, 30, 45, 60, 90, 120, 180, 240, 360, 480, 720, and 1,440 minutes for intravenous doses and 0, 15, 30, 45, 60, 90, 120, 150, 180, 240, 300, 360, 480, 720, and 1,440 minutes for oral doses
	Urine; sufficient number of intervals to characterize the rate and extent of urinary elimination of the test article
Possible series:	0-2, 2-4, 4-8, 8-12, and 12-24 hours for intravenous and oral doses
Bioanalytical:	Validated assay for plasma and urine specimens from rats to be cross-species validated for specificity, sensitivity, linearity, precision, and accuracy
Stability:	Test article stability in collected specimens to be determined from time of collection to projected time of analysis
Analyses:	Individual analytical runs to include all specimens of a given matrix for a test species or 30 plasma unknowns per run
Timeline:	Projected start date
	Estimated completion date

for each research study to be outsourced. This effort can be substantially reduced by the placement of more than one study at a CRO. Many biotechnology companies and some pharmaceutical firms use consultants or consulting firms to assist them in the CRO selection process. However, these firms need to ensure that the consultants have both expertise in scientific disciplines for the studies being outsourced and knowledge of how CROs operate. A common mistake is to hire consultants with expertise in the disease area of the drug candidate but not in the nonclinical drug development process, or conversely, in regulatory compliance but not in the science necessary to successfully characterize a drug candidate. The sponsor should evaluate and select consultants who have the necessary knowledge of drug development and contract research to enhance the chance of a successful outsourcing program.

Pharmaceutical and biotechnology companies commonly use one of three strategies to identify CROs. These strategies can be designated virtual company, preselected, and special study.

1. *Virtual Company Strategy*

The virtual company strategy is used by companies, mostly biotechnology firms and many United States and European subsidiaries of Japanese pharmaceutical firms, that do not have the infrastructure or resources to conduct GLP-regulated nonclinical research studies necessary to support regulatory agency submissions. The primary benefit of this outsourcing approach is that the various expertises, such as toxicologist, pathologist, and drug metabolism expert, and the infrastructure, such as facilities, quality assurance, and GLP compliance, needed to support regulated studies can be devoted to completing nonclinical development studies. This means the sponsoring company does not have to build the inhouse groups and facilities and thus can avoid costly time delays. A primary limitation to this strategy is that the sponsoring company can be vulnerable to poor CRO selection or to mismanagement by the CRO. However, by using experts or consultants appropriately to assist in the identification and selection process and the monitoring aspects, discussed in the following section, a sponsor can usually avoid this limitation.

2. *Preselected Strategy*

In the preselected strategy, the first choice of many large and midsized pharmaceutical houses, a limited number—usually three to six—of CROs are prequalified to support a company's possible nonclinical drug development needs. The qualification process usually includes a detailed site visit to review the CRO's facilities, staff, and GLP compliance and to determine which types of nonclinical research studies, such as toxicology, drug metabolism, and formulation development, can be placed at the CRO. At times, long-term contracts are defined in which the CRO guarantees the sponsoring company a certain level of resources to be available to support projects, and the company guarantees to provide a sufficient number of research studies to effectively use the committed resources. This strategy can provide a synergistic working relationship between the sponsoring company and the CRO, which in essence becomes an integral part of the development processes of the sponsor. The major drawback to the preselected CRO strategy is the unnecessary limitation of outsourcing. If a fairly large number of CROs, say 30, have the necessary expertise to conduct a nonclinical study or group of studies but the sponsoring company prequalified list contains only three CROs with the required expertise, the other 27 are not considered, even though some may be able complete the studies faster and cheaper or may have superior expertise and experience in the drug candidate's therapeutic area.

3. *Special Study Strategy*

The final strategy, the special study strategy, is used by some sponsoring companies to place single or a few nonclinical research studies with a CRO. If a company's internal resources are usually, but not always, sufficient to meet their nonclinical drug development needs, this strategy provides a means to have a critical study completed to meet the timeline on a drug development plan. However, some companies use the special study strategy for all their nonclinical drug development needs and then attempt to integrate the results for the independent studies into a drug development story. For a company with substantial drug development expertise, this strategy may work but requires considerable effort in identifying and selecting CROs, in monitoring the various CROs, and in synthesizing the results from the various research studies. Contract research organizations are generally not in favor of this strategy because they become only "a pair of hands," have little understanding of the overall development program, and thus cannot provide the sponsoring company with their considerable expertise.

Whichever strategy is used, the sponsor should carefully select the CRO to conduct a nonclinical drug development study. One poorly conducted study can delay the drug development process until the study has been repeated and the results integrated into the overall story. If this delay is for a research study on the critical path, the projected time for regulatory agency submission has to be changed, thus delaying the date of approval for marketing and resulting in lost revenue for the sponsoring company.

B. CRO Monitoring

The identification and selection process is only the first step. The second aspect involves monitoring the CROs to ensure that the research studies are conducted according to the study protocol, that the results are obtained with appropriate techniques and procedures, and that the generated data are correctly recorded and documented in the study report. Monitoring studies at CROs should include, but is not limited to:

1. Reviewing and approving the study protocols prepared by the CROs and detailing the procedures to be followed to complete the study designs. The study protocol should provide information on all aspects of the study. Commonly included items in a study protocol are listed in Table 2.

2. Monitoring various aspects during the research phase of each study. Each item listed in Table 2 is a possible point for potential study monitoring. Monitoring will ensure that the data collected are appropriately documented and do not contain "surprises" that can prevent the results from being used to support submissions to regulatory agencies.

3. Assisting in the evaluation and interpretation of results to ensure that the data are analytically acceptable and correctly correlated to tell the story of the experimental results.

4. Reviewing technical reports to ensure that the information provided accurately reflects the generated results, documents any deviation from the study protocols, and gives appropriate conclusions.

The number of person-hours required to appropriately monitor a research

Table 2 Nonclinical Study Protocol Items Commonly Included in a CRO-Conducted Research Study

Protocol Title:	Descriptive title of the nonclinical research study
Objective:	Purpose of conducting the study
Study Location:	Where and by whom the study is to be conducted
Sponsor:	Company that is sponsoring the study
Study Monitor:	Sponsor's agent who is responsible for monitoring the study
Personnel:	CRO senior staff who will be responsible for the various aspects of the study
Study Dates:	Dates when the study is scheduled to be initiated, when the inlife phase is to be completed, and when the draft final report will be available for review
Compliance:	Statements on which regulatory guidelines, such as 21 CFR 58 for FDA GLP compliance, will be followed and on Animal Care Committee protocol review
Test Article:	Information on the drug substance, which commonly includes the test article name or number, identification criteria, physical description, who is responsible for test article characterization, the concentration(s) to be used, recommended storage conditions, inventory maintenance, formulation procedures, reserve samples, retention samples, analyses for content and homogeneity (if necessary), disposition, and safety precautions
Test Species:	Information on the animal species to be studied, animal husbandry procedures, such as housing, food, water, contaminants, environment conditions, acclimation, and justification of selection
Study Design:	Description of the number of test species groups, the dosage level to be administered to each group, the test article concentration or amount to be administered, the number of animals of each sex in each dose group
Assignment:	Statement on how animals will be assigned or randomized to each of the dose groups
Dose Preparation:	Description of how the test article will be prepared for administration to the test species
Route of Dosing:	Statements on how the test article will be administered to the test species, the frequency of dosing, and a justification for the selected route and dose levels
Clinical Observations:	Descriptions on how frequently the test species will be observed and what specific clinical signs are to be recorded in addition to unspecified signs
Body Weights:	Information on how often the test species will be weighed during the inlife phase of the study
Food Consumption:	Information on how food consumption will be determined

Table 2 Continued

Physical Exam:	Description of how often physical examinations will be conducted and by whom
Blood Collection:	Information on when blood specimens will be collected for hematology, clinical chemistry, and toxicokinetics
Hematology:	Description of hematology tests to be conducted on collected blood specimens
Clinical Chemistry:	Description of clinical chemistry parameters to be determined in collected blood specimens
Toxicokinetics:	Description of how blood specimens are to be processed and analyzed for test article concentration, including information on the testing laboratory, assay procedure, and storage and shipping procedures
Euthanasia:	Information on how the test species will be sacrificed at the end of the inlife phase of the study
Moribund or Found-Dead Animals:	Statements on how animals found moribund or dead during the inlife phase will be handled
Necropsy:	Information on the procedures to be used during necropsy
Organ Weights:	Description on which organs are to be weighed and the procedures used to prepare organs for weighing and fixing for histopathologic examination
Histopathology:	Statements on which tissues will be examined and how the information will be recorded by the pathologist doing the reading
Statistical Analysis:	Information on the statistical tests that will be performed on the collected results
Reports:	Description of what information will be included in the study report to be submitted to the sponsor
Raw Data:	Information on how, where, and for how long raw data will be stored
Approvals:	Signatures of a sponsor representative, commonly the study monitor, the study director, and a corporate officer of the CRO

study conducted by a CRO again depends on the size of the research program. Normally, a minimum of 1 person-week for each in-life phase month of a research study is required and includes the time necessary to review and approve the study report. As noted above, some firms use consultants or consulting firms to assist with CRO monitoring and to ensure that the studies were conducted according to GLP guidelines. These consultants should be specialists in the scientific disciplines for the conducted studies. Having a toxicologist or pharmacologist consultant monitor the bioanalytical chemistry program to support a pharmacokinetic research study could result in an assay that is inappropriately validated and thus not capable of analyzing specimens for drug and drug metabolite concentrations.

III. CONCLUSION

This chapter has provided information on the selection and monitoring aspects of conducting research studies at CROs. By carefully evaluating and selecting CROs and then monitoring them during and after the study, the sponsoring firm can obtain the information needed to successfully characterize their drug candidate and prepare the necessary submissions to regulatory agencies. A close partnering between the sponsor or its designated agents and the CRO is very important to ensure that the research studies are conducted as designed and within the planned time frame.

PART II. CLINICAL CONTRACT RESEARCH ORGANIZATIONS

I. INTRODUCTION

The clinical portion of a drug development program constitutes the most labor-intensive and costly phase of drug development. It is not unusual for even the large pharmaceutical companies to find themselves understaffed to embrace some aspects of a particular clinical development program, and the need is even more acute in most small biotechnology companies. If senior management in the sponsor company is not willing to support permanent increases in staff to accommodate the program's needs, or if sufficient numbers of qualified staff cannot be recruited and hired soon enough, the sponsor company will turn to a CRO for the solution. The trend is increasingly in this direction, and thus managers and directors of clinical programs must adapt to this new way of conducting programs.

When properly managed, CRO services can provide a cost-effective solution and thereby enhance the ability of the sponsor team to achieve the corporate goals that are typically defined by time and budget constraints. However, if the relationship is mismanaged, valuable time and money will be wasted. A common reason for failure is ineffective communication. Effective communication between the sponsor and CRO must occur at all stages of the relationship, including:

1. At the onset when the scope of the project is being defined and a CRO is being chosen
2. During the conduct of the project

Each of these phases of the relationship will be discussed in turn, with an emphasis on ways to achieve effective communication and a successful relationship.

II. DEFINING THE SCOPE AND CHOOSING A CRO

An entire clinical development program usually spans several years and includes many individual studies. Most sponsors will use CROs for some portion of the clinical development program, but rarely for creating the overall development plan. Nevertheless, if a particular CRO has established experience in a particular therapeutic area, it may be helpful in providing an independent assessment of draft plans prepared by the sponsor.

Contract research organizations can provide services for clinical trials whether they are the simplest phase 1 safety and tolerance studies or complex multicenter phase 3 efficacy and safety studies. Table 3 identifies specific activities that may be considered for outsourcing. These activities are grouped according to four major categories: management of the study conduct at clinical sites, data management, data evaluation, and summarization.

The scope of the work to be outsourced is driven by the specific needs of

Table 3 Scoping Out the Project

Prepare or Review Overall Clinical Development Plan
Management of clinical study conduct
Protocol writing
Site selection
Investigator meetings
Monitoring
-site initiations and close-outs
-primary and secondary monitoring
GCP audits
Data management
Case report form design
Database design
Data entry
Data evaluation
Programming for data listings and summary tables
Statistical analyses and interpretation
Data summarization
Medical interpretation
Medical writing

the sponsor. In some instances all aspects of a particular study will need to be outsourced. In other instances, CROs are needed to provide only specific services to complement an almost complete team within the sponsor company. The bulk of the contracts awarded to CROs deal with one or more of the most labor-intensive portions of clinical research, namely, clinical monitoring of study sites, data entry, programming for data listings and summary tables, and writing clinical study reports.

Whatever the scope of the project, clear communication of the exact work plan is enhanced by providing a detailed description of the activities and the expectations. Merely listing activities, as presented in Table 3, is grossly inadequate and will result in numerous iterations in contract proposals as the CROs request more specific instructions and rework their proposals accordingly. Some questions to be considered when providing details of the work plan and deciding which CRO to select are as follows:

1. Does the CRO have experience in the particular therapeutic area under development? This is not always an absolute requirement, but it is a strength when comparing CROs.
2. Does the CRO have access to the patient population needed for the trial? For example, some CROs maintain specific patient pools, such as patients with hepatic impairment or renal impairment, often needed for clinical pharmacology studies.
3. If the study being outsourced is a pharmacokinetic or clinical pharmacology study, does the CRO have analytical laboratory facilities and expertise appropriate for the analysis of blood samples? Can your analytical methods be transferred to their laboratories and validated or will samples be shipped to the sponsor for analysis?
4. If the CRO is to prepare the detailed clinical protocol, are there other protocols from the same program that can be used as a template?
5. Do you want the CRO to assist or participate in the investigator meeting?
6. If the CRO will be monitoring the study, will they be doing all of the monitoring for all sites, or will some sponsor personnel also be monitoring?
7. If the trial is international, can the CRO provide monitoring services (or other services) in all jurisdictions? If it is decided to work with separate CROs in each country, be sure to recognize the sponsor effort needed for coordination of all CROs.
8. Will the CRO be providing primary or secondary monitoring, or both?
9. When will the CRO get involved with sites—before site initiation or after selection and initiation are completed by the sponsor?
10. Who will be negotiating the investigator grants for each clinical site, the CRO or the sponsor?

11. Will the CRO be asked to conduct GLP audits for selected clinical sites?

12. If the CRO is to design the case report forms, is there a set from a similar study that can be used as a template?

13. If the CRO will be asked to design the database, will they need to standardize certain aspects with existing databases to allow them to be combined later? If so, provide some details on required structure.

14. Have data conventions been established for other studies in the clinical program that will need to be followed for this new study?

15. What are the standard procedures of the CRO for handling queries and corrections to the database?

16. What audit trail will be created to document data conventions and database corrections?

17. Has the CRO ever been audited by FDA?

18. Will an independent GCP audit of the CRO's activities be undertaken?

19. If the CRO is being asked to program data listings and summary tables, how many such listings and tables are expected? Do templates or examples exist from other clinical studies in the same program?

20. Are the final deliverables clear to all parties? For example, do you expect to receive the programs (for example the SAS code) used to run the statistical analyses?

21. Does the CRO have experienced staff to provide statistical or medical interpretation of the data?

22. If the CRO is to write the clinical study report, does the sponsor have a standard template to be followed?

23. What word processing program is required? What are the expectations regarding in-text tables? Can they be imported directly from SAS, for example, or will significant word processing be required for new formats?

24. How many drafts are expected for a study report?

25. What are the time constraints for the activities being outsourced? Which dates are not negotiable? Which are subject to some flexibility?

26. Can the CRO offer assurance that personnel will be dedicated to your project?

27. What is the experience level of the specific individuals who will be assigned to your project?

28. Can the CRO provide names of previous customers with whom you can speak directly and privately?

29. What are the provisions in the proposed contract that deal with cost overruns and substantial increases in workload above what was originally anticipated?

30. What are the procedures for changing the scope of the project?

31. Does the CRO have the capacity to add more resources to the project if necessary?

32. How important is this project to the CRO? Is there a risk that your project will suffer because of competition for resources for higher status projects from other companies?

33. What are the provisions in the contract for dealing with poor performance?

34. Are the financial terms of the contract acceptable to the sponsor? How much is paid up front versus upon completion of major milestones?

35. Should the financial terms include penalties for significantly missed milestones or incentives for milestones completed ahead of schedule?

36. If the CRO is providing only selected activities to support a clinical study, how will the overall project be managed? Will a formal joint team be established with regular meetings?

37. How frequently will status reports be required from the CRO? Do these reports need to be written or verbal?

38. Will all contact be directed through one person in the sponsor company? How accessible to the CRO will other key personnel in the sponsor company be?

III. WORKING WITH THE CRO

The start-up of the relationship requires a considerable amount of time from sponsor personnel to ensure that the scope of the work is fully understood and that standards are clear. This highly interactive phase of the relationship may be ill-timed, unfortunately, because most companies decide to use CROs only after all possibilities of using internal resources have been exhausted, which often means that the sponsor personnel themselves are exhausted too! The sponsor staff may have a tremendous desire to "hand off" the project completely and as quickly as possible to the CRO, but this will not be in the best interest of the project.

Whereas working with a CRO can be an efficient way to expand the project's human resources rapidly, one must recognize that internal resources still will be needed. With such significant investments in clinical programs, it would be penny-wise and pound foolish for sponsor management not to ensure that sufficient personnel exist inhouse to oversee the performance of the CRO.

Usually one individual in the CRO and one in the sponsor company are given project management responsibilities for the contract activities. However, this should not be interpreted narrowly to mean that all communication must go through these two individuals. Other individuals in each organization should have direct access to their counterparts in the other company for clarification of specific details. Joint working teams that discuss the details of the project at the level of implementation will enhance the quality of the communication between companies and increase the likelihood of the project's success.

The most effective working relationships are forged when the sponsor views the CRO staff as an extension of its own inhouse team. If the CRO is providing supplemental services to complement an inhouse study team (for example, providing additional clinical monitors or handling the data management and statistics for a trial that is monitored by the sponsor), then regularly scheduled joint team meetings will foster effective communication and standardization of efforts. Face-to-face meetings are ideal, but not always possible, given the geographic distances existing between some parties. Teleconferences and videoconferences can be very effective. If the CRO is responsible for the entire conduct of a study, then regular update meetings are necessary to review progress and modify the activities as necessary to the achieve the time and cost goals.

Even with the best intentions and careful review of the contract, either party may find that part of the way through the conduct of the activities it is necessary to revise the scope and perhaps the timeline and cost estimates. Provisions for how to approach such discussions should be provided in the contract, and these discussions may be best handled by senior management in both companies to preserve the working relationships of the members of any joint working teams.

Returning to the clinical activities listed in Table 3, some thoughts on the level of support that is realistic to obtain from CROs are as follows. A number of the labor-intensive activities, such as monitoring, auditing, database management, programming for listings and tables, and statistical interpretation are relatively easy to outsource, and many CROs will have the necessary experience and capacity.

Protocol writing and case report form design go hand in hand, and most CROs have the capability to handle these activities. But the sponsor should lead the strategic discussions on the study design and the statistical plan, taking into consideration the overall clinical development plan, which may include other indications, and the commercial objectives of the company. A high level of sponsor involvement in designing the study will increase the "ownership" of the project by the internal clinical team, even if 95% of the activities for running the trial are handled by contract services. This ownership is important to maintain throughout the trial because in the end, it will be the sponsor personnel who will be defending the data to regulatory authorities such as the FDA.

Some CROs can be very helpful in identifying qualified clinical sites if they have previous experience in a particular therapeutic area. This can be of great use to small companies that are just starting new development programs.

The process of data summarization, encompassing both medical interpretation and medical writing, can be one of the more challenging aspects of a clinical program. The greater the level of sponsor involvement in these activities, the more internal ownership is reinforced and the sponsor is better able to defend the data. That is not to say that CROs cannot play an important role in this step. Contract research organizations that have medically trained personnel with expertise in particular therapeutic areas can be an excellent resource for small companies that may have no internal medical staff.

Highly skilled medical writers are currently a limited commodity and difficult to recruit for most companies. Furthermore, the writing process itself is very time consuming. For both of these reasons, companies are seeking these experts more and more through contract services. If the sponsor has no medical writers, then it might be best to have the CRO complete the report, seeking medical interpretation from the sponsor clinical team as necessary. If the sponsor does have experienced medical writers, but the volume of work is too much, then a CRO could provide valuable assistance for the most labor-intensive parts of the writing, for example, by providing first and second drafts of the report. The sponsor team could then take over the report and provide the finishing "polish" on the interpretation of the data and standardization with reports for other trials in the same program.

IV. CONCLUSION

A effective relationship with a CRO is, in some ways, like a marriage. The key to success is open and honest communication, clear division of responsibilities, and patience while the relationship evolves into maturity. Once a match has been made, knowledge acquired in the first successful project can carry forward to subsequent contracts, and efficiencies are realized for both organizations. Many companies are finding it to their advantage to consider long-term relationships with desirable CROs, in which both parties provide some level of commitment to future projects, even before the exact details of those projects are known. Both parties benefit from such arrangements. The CRO can better manage personnel requirements when future contracts are guaranteed, and the sponsor has the security of knowing that qualified resources will be available.

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The Evolving SMO in the United States

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I. INTRODUCTION

During the past several years, industry has had to swallow a bitter pill: despite the streamlining of operations and a dramatic increase in outsourcing, the speed with which companies develop drugs and introduce them into the marketplace has not improved. The traditional collaborative process, where the sponsor and CRO place and manage development projects among a fragmented and unsophisticated base of investigative sites, has proven inefficient and slow. Although regulatory review times have declined 6% annually since 1992, development cycle times have not come down in that same period because of rising project complexity and scope.

It is now widely believed that the greatest impact on reducing development cycle time will come from more effective conduct of clinical trials—in essence, at the point at which patients are recruited and clinical data are collected. The study conduct arena offers many opportunities for incremental improvement, from site selection through IRB approval, patient recruitment and enrollment, and data collection.

Sponsors are aggressively seeking ways to accelerate how studies are implemented and patients enrolled. Financial and performance pressures from sponsors and CROs have changed the economics of the study conduct arena and have raised the caliber of investigative sites now conducting clinical trials. This competitive operating environment, characterized by rapid growth and relatively low barriers to entry, also has led to the formation of innovative study conduct models. From a cottage industry have emerged more business-like and technology-driven, sophisticated, and performance-oriented research centers. The market for contract study conduct services is large and growing at more than 16% annually. CenterWatch estimates that $3.2 billion in clinical grants were allocated to investigative sites in the United States in 1997. For the sponsor and the traditional large CRO, there is a richer and broader range of outsourcing options and alternatives to consider.

Whereas there is great optimism around the market opportunity for new study conduct ventures, there is little information to date suggesting that any particular study conduct model holds a competitive advantage. Currently, the SMO marketplace is an immature one. However, the SMO market is poised to drive rapid industry consolidation with more than $40 million in new venture capital and the entrance of large, publicly traded companies.

To compete more effectively, all segments in the investigative site market—academic medical centers, parttime principal investigators, and full-time dedicated clinical research centers—are rationalizing and improving their approach to conducting clinical studies. These improvements include:

Centralizing clinical research operations
Standardizing contracts and operating procedures
Training and accrediting staff
Adopting new technologies to manage information and to track performance
Managing clinical data more systematically
Streamlining approval times (e.g., IRB and legal)
Reducing fixed costs to offer more competitive pricing
Applying business and management principles

At the same time, new and innovative businesses have entered the clinical trials industry with hopes to improve study conduct efficiencies and effectiveness.

II. BROKERS AND MOBILE AND VIRTUAL SERVICE PROVIDERS

A number of individuals and organizations offer brokering services in which they act as a business development agent for a group or network of investigative sites. The broker or agent will develop marketing communications and pursue grant opportunities. Typically, a sponsor or CRO will contact these agents for a list of potential candidates to conduct their trials. The agent will receive a finder's fee, and then typically leaves it to the site and the sponsor or CRO to initiate and conduct the project.

In the past several years, contract service providers have emerged that centralize a specific niche activity within the overall study conduct process.

Several organizations, for example, offer trained study coordinators through a central corporate enterprise. These companies typically secure the grants and use their network of study coordinators to conduct the studies. Some of these organizations own their facilities and hire the principal investigators. Others contract with area physicians to manage clinical trials within the physician's practice.

These service providers hope to offer sponsors efficiencies and cost savings through the improvement of a specific study conduct responsibility. The major weakness in these services is that they lack management controls over the principal investigator, the research facility, and the investigative site personnel. These providers are essentially only enhancing a part of the total study conduct process and, therefore, have only a limited impact on the overall process. In addition, there is some criticism that these providers lack the ability to transfer efficiencies across projects. Each time a study is initiated, these providers must often reinvent the wheel.

III. SITE MANAGEMENT ORGANIZATIONS—THE CONSOLIDATION AND INTEGRATION PROVIDERS

Given the rich variety of study conduct business models emerging to fill market needs, industry has had a hard time reaching a consensus around a definition of the SMO. As one industry spokesman puts it, "If you've seen one SMO, you've seen . . . well . . . one SMO."

The following are general SMO characteristics:

1. They are business enterprises with multiple study conduct locations (regional and national).
2. They are managed centrally by a corporate structure.
3. They offer a full range of study conduct services, including, at times, both project management and study conduct services.
4. They focus on providing two primary assets: a large and diverse group of physicians and patients and clean clinical study data.

Site management organizations have aggressive aims to re-engineer and overhaul the clinical development process through consolidating the fragmented and unsophisticated market for site services. They hope to offer sponsors and CROs access to a consolidated base of investigators, quicker study start-up, faster time to study completion, and cleaner data. A major aspect of an SMO's strategy is to leverage various information technologies to improve the capture rate and management control of study data.

The corporate offices of SMOs typically handle a wide range of study conduct activities that are best provided through a systematic and centralized approach. These activities include regulatory and legal affairs, sales and marketing, business development, strategic planning and market research, contract and budget negotiations and approval, patient recruitment, and management operations (e.g., administrative, finance, IS, and human resources).

The traditional approach to monitoring has proved greatly inefficient. The typical study monitor travels as much as 75% of the time. This leads to "CRA burnout" and the challenge of replacing and training new CRA staff. Most importantly, it leads to costly delays related to poor data monitoring, interpretation, and follow-up. Site management organizations and site networks are looking at new approaches, through the use of technologies and internal staffing, to improve site monitoring effectiveness. Regionally based inhouse staff to provide monitoring services and advanced auditing and data capture technologies are approaches being used.

At this time, there are between 20 and 40 SMOs with aspirations to become national in scope. This group holds a 4% to 5% share of the total $3.2 billion clinical grants market at present. Individuals driving the SMO concept are entrepreneurs—some business people, others scientists—and they are offering consolidated and integrated study conduct services in a variety of ways. Each approach possesses core strengths and weaknesses. The SMOs—consolidation and integration providers—fall into four organizational models:

1. Corporate model
2. Physician-owned affiliation model
3. Loose affiliation model
4. The hybrid model

A. The Corporate Model

The SMOs in this group own and operate the sites in their network. These providers primarily vary by whether each site in its network has a staff physician serving as the principal investigator, or whether the center primarily contracts with area physicians to fill the role of the principal investigators. Corporate-owned SMO providers that do not have staff medical directors will typically staff each of their centers with a site manager, study coordinator(s), and, lately, patient recruitment specialists. Physicians are paid on a fee-for-service or hourly basis. Depending on the trial, patients are seen either at the physician's office or at the SMO's own facilities.

Wholly owned SMOs recruit patients through the contract physician's database, but must also rely on media advertising and their own patient data bases, particularly if physicians are on staff and not maintaining a clinical practice.

The perceived strength of corporate-owned SMOs is the ability to control all aspects of the study-conduct process. Because the sites are owned, the company can manage operating centrally to ensure that the sites in its network meet the performance standards. The investigative sites share a common mission: to treat clinical research as a business. Site personnel are company employees. In addition, this model may offer higher profit margins.

One major weakness of the corporate or wholly owned SMO, relative to other SMO models, is its access to patients. Sites must advertise for a high percentage of patients, which can be both time consuming and costly. Patients identified through the use of broad-based media may be less attractive to sponsors, who often prefer to test their drugs among "real patients" being treated in the context of regular clinical care. This model may pose higher fixed costs.

Another weakness applies to the corporate-owned SMOs that contract with area physicians. Although these providers are able to tap into a larger community of physicians, the investigators do not become part of the company's core resources.

Examples of corporate or owned-site models include Hill Top Research, Protocare, and Radiant Research.

B. Physician-Owned Affiliation Model

In order to join a physician-owned SMO, physicians typically purchase stock in the company. These physicians then share in the profits of the business and if these SMOs enter the public markets, physician-owners stand to gain a considerable return on their initial investment.

The strength of this model is that investigators are practicing physicians. In terms of patient recruitment, this type of SMO has access to a greater number of patients through its members' patient databases. The SMO may supplement this core resource with advertising and its own corporate database, but the majority of the patients are likely to come from the physicians' own patient community.

The SMO can draw on its members' scientific expertise to provide the sponsor with protocol design services. For this reason, most of the physician-owned SMOs have their origins in a specific therapeutic area. During the past several years, physician-owned SMOs have emerged in areas that include urology, neurology, psychiatry, rheumatology, and infectious diseases. By contrast, corporate or wholly owned SMOs have been largely multispecialty.

Physician-owned SMOs also offer sponsors an opportunity to hire physicians who are involved in providing direct patient care. Investigators from these networks can provide insights and feedback into how the investigational drug might be integrated into a patient's overall health program.

A major weakness of the physician-owned SMO is that the company doesn't have tight control of its study conduct operations being carried out at each investigative site in the network. The common difficulties in managing physicians has been well documented in a variety of settings, including HMOs, PPOs, and PPM groups. Study coordinators are employed by the investigator and hence are more difficult for a central office to manage. Because investigators and their staffs receive revenue from their clinical practices, there is also some question about their commitment and motivation to be top performers in conducting clinical studies.

This lack of control can make it difficult for physician-owned SMOs to ensure quality performance across all sites. If a site is slow to enroll patients or generating CRFs with a high incidence of errors, physician-owned SMOs are not necessarily empowered to quickly improve an individual site's performance. This is particularly troublesome in light of the fact that in a large multicenter trial, success hinges on the worst-performing site. Data cannot be locked and analyzed until all the sites are closed. Physician-owned SMOs may not have the same ability to conduct studies quickly and produce clean data as do the wholly owned SMOs.

Examples of physician-owned models include Affiliated Research Centers and Rheumatology Research International.

C. Loose Affiliation Model

In loosely affiliated site network SMOs, the corporate office identifies, negotiates, and secures study grants, and typically provides a variety of management services, including marketing and sales support, information systems support, and staff training. However, the investigators do not have an ownership stake, nor do they have exclusive arrangements with the corporate SMO. Investigative sites in these networks may secure most of their grants directly from their own contacts within sponsors and CRO companies.

The key strength of the loosely affiliated network SMO is its size. These SMOs have access to a large number of investigative sites. Because the relationship to its investigators is a nonexclusive one, the loosely affiliated networks can sign up many sites, and therefore have the potential to grow quickly with minimal capital investment. In this way, as sponsors' development needs change, the loosely affiliated network SMO may respond faster than other SMO models. The weakness in the loosely affiliated network SMOs is an even greater lack of control over the performance of each site in its network.

D. The Hybrid Model

The hybrid SMOs are establishing a position as providers of fully integrated contract clinical research services. Typically driven by CROs eager to enter the study conduct market, hybrid SMOs provide CRO services and own and operate study conduct centers. Traditional CRO activities like protocol design, project management, site monitoring, and data management are offered in conjunction with traditional site services like study initiation, patient recruitment, and data capture services. It is through this integration that hybrids hope to offer truly accelerated clinical development services.

Hybrid SMOs believe that inefficiencies exist within the study conduct arena and between project management and study conduct functions. The hybrid SMO promises to apply management controls across a broad range of clinical development activities—from project planning through implementation and NDA submission. It is this seamless integration that hybrid SMOs believe will be a competitive advantage in the long term.

Only a handful of providers are pursuing this approach. Two midsized CROs and several small CROs currently own and operate site networks. There are a number of criticisms of the hybrid SMO approach. Several industry observers have commented that project management and study conduct services require unique and distinct skill sets that cannot be integrated. Others argue that the hybrid SMO has been slow to catch on, because a conflict of interest exists when investigative sites are monitored by the same company that owns them. Several industry observers believe the hybrid SMO will be unable to pursue a sizable portion of the overall clinical grants market because it competes with traditional CROs that are reluctant to place studies there. Therefore, the hybrid SMO may have constrained growth potential.

Interestingly, many large and midsized CROs have formed, or are in the process of forming, alliances with various investigative sites. In so doing, these CROs are moving in the direction of offering hybrid SMO services. Under this type of arrangement, the ability of the CRO to control and improve study conduct performance is weakened.

CRO-SMO hybrid examples include Scirex, INC Research, MDS Harris, and Ingenix.

E. AMCs and the New Entrants-PPMs and Integrated Health Systems

Academic medical centers have been slower to adapt to the current operating environment for industry-sponsored clinical research, yet more than 25 medical schools have established central offices for clinical research or are in the process of doing so. Most AMCs committed to conducting industry-sponsored clinical research are seeking ways to shorten IRB, contract, and legal review times. Not unlike the for-profit SMO, many AMCs are offering investigator and site selection services, investigator and coordinator training, contract and budget negotiation services, and marketing and business development support. Several AMCs (including Duke, Columbia, and the University of Rochester) are now capable of competing effectively with top performing investigative sites in the for-profit sector.

As the health care marketplace evolves, the risk and control over the delivery and the quality of patient care is shifting back to the physician. Managed care organizations are increasingly playing the role of health insurance providers. Physicians are reasserting their influence and organizing into larger group practices and PPMs with large patient populations and prescription volume. Though in their early stages, integrated health care systems composed of a variety of delivery approaches within academic medical centers, acute care hospitals, community clinics, and HMOs are forming, and they too offer large and diverse physician and patient populations.

In clinical research, there is no question that investigative site performance, quality, and speed, combined with competitive costs, are the ultimate determinants of success. How important a role will the size and scope of a study conduct provider's access to physicians and patients play in the sponsor and CRO's site selection process? Site management organizations are aggressively seeking ways to expand their networks of sites. Large health care consolidators, offering incomparable numbers of patient and physicians, present compelling models of study conduct. In the next several years, top performing sites, independent, network, and SMO models, will no doubt aspire to play more active roles in managing their clinical trials operations within larger integration system settings; several site networks and SMOs will likely be assimilated into larger systems; and others will more closely align themselves with PPMs and other integrated enterprises.

Sponsors and CROs are looking for study conduct providers that offer fewer-stop shopping, combined with highly effective patient recruitment and retention, and ease of entry and market penetration. As a result, the following are becoming increasingly important site selection criteria:

A large, diverse, and loyal patient population
A motivated and experienced clinical staff (e.g., physicians, coordinators)
A representative, actual-use health care setting
An efficient business operation
Well-managed and maintained longitudinal patient records
Financial stability

IV. CONCLUSIONS

At present, sponsors and CROs do not completely understand, nor do they fully embrace, the SMO and hybrid concepts. The scope of most major clinical development projects often prevents sponsors and CROs from ever using SMOs as one-stop sources for study conduct services.

Sponsors and CROs are actively developing ways to manage their outsourcing practices more rationally and systematically. As limited SMO performance data exist, it is difficult for sponsors and CROs to evaluate quantitatively their outsourcing options.

The next couple of years will be an important period for SMOs to demonstrate clearly their ability to accelerate timelines and improve data quality. The SMOs are aggressively looking to steal market share from poor performers. The heads of some of the largest SMOs anticipate controlling as much as 40% of the market for study conduct services within the next 5 years. Contract research organizations especially are unsure how to respond to the emergence of the SMO. Are they to be seen as partners or as potential competitors? At least in the short term, most observers believe that CROs can use the benefits of the SMO while SMO providers successfully carve out the market for study-conduct services. The industry is growing rapidly, and there is certain to be market demand for companies that can organize site services, conduct trials quickly, and provide high-quality data.

Ultimately, sponsors and CROs will turn to a project's specific development strategy and plan to determine how best to use the rich variety of outsourcing options available. Much like fund managers who maintain a dynamic portfolio of assets, sponsors and CROs will need to become more proactive and proficient at managing intelligently and strategically their outsourced services partners. In the long run, the exciting outsourcing alternatives offer great promise for reducing development cycle times and improving quality.

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